# FLAME: Taking the good things without the downsides

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Dose escalation in prostate cancer has been a double-edged sword. On the one hand, it leads to improved freedom from biochemical failure (FFBF), but on the other, the increased doses to normal tissues result in an increase of gastrointestinal or urogenital toxicity (1-3). It has never been proven that FFBF translates into improved rates of distant metastasis-free survival (DMFS), cancer-specific survival (CSS) or overall survival (OS) (1-3); therefore, many consider that further dose escalation is of questionable benefit. However, the FFBF endpoint is certainly useful, as a disease relapse eventually may require additional treatments that have associated toxicities and costs, as well as psychological discomfort of patients.

Kerkmeijer et al. reported the results of a novel dose escalation approach (4). The focal lesion ablative microboost in prostate cancer (FLAME) phase III trial presented the outcome results of an isotoxic dose escalation approach in 571 intermediate or high-risk, node-negative, prostate cancer patients (4). The approach consisted of a focal boost to the gross tumour volume as defined by multiparametric MRI, with dose escalation up to 95Gy (115.8Gy equivalent total doses in 2Gy fractions (EQD2)) when possible. The approach was isotoxic, meaning that specified dose constraints to the organs at risk were strictly adhered to, and this resulted in reductions of boost doses when required. The arms were well balanced; 35% of patients did not receive hormonal treatment in each arm. The median follow-up was 72 months. The primary endpoint FFBF at five years was significantly improved from 85% (77Gy in 35 fractions or 81.8Gy EQD2, standard arm) to 92% (focal boost arm). The hazard rates for FFBF remained significant after adjustment for hormonal treatment duration, as they did for the timing of hormonal treatment, among other factors such as T-stage, initial levels of prostate-specific antigen (ng/ml), Gleason Score and centre. In the focal boost arm, 99% of tumours were treated with a dose escalation over 82.4Gy, and the median tumour D50% and D98% were 93Gy and 84.7Gy respectively (5). Importantly, although differences in DMFS rates were not significant, the data seemed to suggest a dose response relationship of reduced levels of distant metastatic failure with increasing boost doses at seven years. Differences in late genitourinary and gastrointestinal toxicity, as well as health related quality of life, were not significantly different between the two arms.

To conclude, this trial has shown that MRI-guided isotoxic dose escalation, which can be performed with standard modern radiotherapy equipment (intensity-modulated radiotherapy/volumetrically modulated arc therapy), improves cure rates in intermediate and high-risk prostate cancer patients, but without increasing toxicity. The results are likely, therefore, to lead to changes in clinical practice.

1. 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 80:1056-1063, 2011
2. 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 70:67-74, 2008
3. Al-Mamgani A, van Putten WL, Heemsbergen WD, et al: Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 72:980-988, 2008
4. Kerkmeijer LWG, Groen VH, MD, Pos F, et al. Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial J Clin Oncol 39:787-796, 2021

5. van Schie MA, Janssen TM, Eekhout D, et al.Knowledge-Based Assessment of Focal Dose Escalation Treatment Plans in Prostate Cancer. Int J Radiat Oncol Biol Phys 108(4):1055-1062, 2020