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Citation
Draulans, C., Haustermans, K., Pos, F. J., Heide, U. A. van der, Cock, L. de, Zyp, J. V. van, … Kerkmeijer, L. G. W. (2024). Stereotactic body radiotherapy with a focal boost to the intraprostatic tumor for intermediate and high risk prostate cancer: 5-year efficacy and toxicity in the hypo-FLAME trial. *Radiotherapy & Oncology*, *201*. doi:10.1016/j.radonc.2024.110568

Version:	Publisher's Version
License:	Licensed under Article 25fa Copyright Act/Law (Amendment Taverne)
Downloaded from:	https://hdl.handle.net/1887/4209177

Note: To cite this publication please use the final published version (if applicable).

Radiotherapy and Oncology 201 (2024) 110568

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Stereotactic body radiotherapy with a focal boost to the intraprostatic tumor for intermediate and high risk prostate cancer: 5-year efficacy and toxicity in the hypo-FLAME trial

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A B S T R A C T

Background: The addition of an integrated focal boost to the intraprostatic lesion is associated with improved biochemical disease-free survival (bDFS) in patients with intermediate- and high-risk prostate cancer (PCa) in conventionally fractionated radiotherapy. Furthermore, whole gland stereotactic body radiotherapy (SBRT) demonstrated to be non-inferior to conventional radiotherapy for low- and intermediate-risk PCa. To investigate the combination of ultra-hypofractionated prostate SBRT with iso-toxic focal boosting for intermediate- and high-risk PCa, we performed the hypo-FLAME trial.
Methods: Patients with intermediate- or high-risk PCa were enrolled in the phase II hypo-FLAME trial. All patients were treated with 35 Gy in 5 weekly fractions to the whole prostate gland with an iso-toxic integrated boost up to 50 Gy to the multiparametric MRI-defined tumor(s). If the dose constraints to the normal tissues would be exceeded, these were prioritised over the focal boost dose. The current analysis reports on the 5-year bDFS, late toxicity and health-related quality of life (HRQoL).
Results: Between 2016 and 2018, 100 men were treated with a median follow-up of 61 months. The estimated 5-year bDFS (95 % CI) was 93 % (86 % to 97 %). At 5 years, the prevalence of grade 2 + genitourinary and gastrointestinal toxicity was 12 % and 4 %, respectively.
Conclusion: Ultra-hypofractionated focal boost SBRT is associated with encouraging biochemical control rates up to 5-year follow-up in patients with intermediate- and high-risk PCa. Furthermore, prostate SBRT with iso-toxic focal boosting is associated with acceptable late genitourinary and gastrointestinal toxicity rates.

Introduction

Prostate cancer (PCa) affects over 1.4 million men each year worldwide [1]. External beam radiotherapy (EBRT) is an appropriate treatment for a large proportion of patients with intermediate- or high-risk PCa. Traditionally the prescribed radiation dose is being delivered by means of 35 – 40 daily treatment sessions, delivering 1.8 – 2.0 Gy per session. In the late 2010s, moderate hypofractionated EBRT, treating patients in about 20 sessions, became a standard treatment for localized PCa based on several phase III trials [2–7]. The positive results of these moderate hypofractionation trials led to a growing interest in ultra-hypofractionation delivering the treatment in about five sessions, using stereotactic body radiation therapy (SBRT). Excellent outcome rates for mainly low- and intermediate-risk PCa patients were obtained by different ultra-hypofractionation trials, including the randomized HYPO-RT-PC and PACE-B trial [8–10]. The 5-year results of the PACE-B trial, showing non-inferiority of a 5-fraction SBRT schedule delivering 36.25 Gy to the whole prostate gland compared to patients treated by a conventionally or moderated hypofractioned scheme, supported ultra-hypofractionated SBRT to become a new standard of care for patients with low- and favorable-intermediate-risk PCa [11]. In addition to a theoretical potential to obtain biological dose escalation because of the low α/β ratio of PCa by using hypofractionation, the financial and logistical advantages of ultra-hypofractionated regimens are major benefits of this strategy, as well as patients' convenience. The question arises whether a 5-fraction SBRT regimen could also be effective in men

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https://doi.org/10.1016/j.radonc.2024.110568
Received 28 August 2024; Received in revised form 25 September 2024; Accepted 27 September 2024
Available online 2 October 2024
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with higher risk PCa.

Based on previous research, it is assumed that higher-risk disease requires higher conventionally fractionated radiation doses for comparable effectiveness [12]. Physical whole-gland dose escalation to 80 Gy and higher, using conventional fractionation delivering 2 Gy per session, led to lower rates of biochemical failure and distant metastases and improved overall survival in patients with high-risk PCa [13–16]. Unfortunately, the positive results of whole-gland dose escalation come often at the cost of increased toxicity [17]. Furthermore, local recurrences are still observed, mostly at the site of the primary tumor [18,19]. The phase III Focal Lesion Ablative Microboost in prostatE cancer (FLAME) trial showed that iso-toxic focal boosting of the intraprostatic tumor(s) up to 95 Gy in addition to EBRT to the whole prostate gland improved biochemical disease-free survival (bDFS) without significantly increasing toxicity or deteriorating health-related quality of life (HRQoL) in patients with intermediate- or high-risk PCa [20]. Both, the non-boosted standard and focal-boosted experimental group were treated by a conventionally fractionated, 35-session, scheme.

By combining physical dose escalation, using the focal boost strategy, with biological dose escalation based on ultra-hypofractionation, one could combine the advantages of both, especially in patients who are at higher risk of disease recurrence. To investigate the delivery of an ablative microboost to the macroscopic tumor(s) within the prostate using ultra-hypofractionation, we performed the hypo-FLAME trial. Early, favourable toxicity results were reported previously [21]. Here, we report the efficacy, clinician-assessed toxicity and patient-reported HRQoL outcomes up to 5 years after treatment.

Material and methods

Study design and participants

The hypo-FLAME trial is a prospective, multicenter, phase II trial conducted at four hospitals, of which three are in the Netherlands, i.e. University Medical Center Utrecht (UMCU) (Utrecht), Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI-AvL) (Amsterdam), and Radboud University Medical Center (RadboudUMC) (Nijmegen), and one in Belgium, i.e. University Hospitals Leuven (UZL) (Leuven). This trial was approved by the institutional ethical review boards of UMCU for the Netherlands (NL53719.041.15a) and UZL for Belgium (B322201731522) and was conducted in accordance with the principles of Good Clinical Practice. The trial is registered with ClinicalTrials.gov as NCT02853110.

The trial recruited patients with PCa who were planned to receive radical EBRT as their primary treatment. Eligible patients were men aged 18 years and older who had World Health Organization (WHO) performance status score 0–2 and histologically confirmed adenocarcinoma of the prostate without evidence of lymph node or distant metastases. Patients were required to be diagnosed with EAU intermediate- or high-risk PCa with at least one of the following risk criteria: clinical T-stage T2b, T2c, T3a or T3b with less than 5 mm invasion in the seminal vesicles on multiparametric MRI (mpMRI) according to the TNM 7th edition; Gleason score of 7 or higher; or iPSA concentration $\geq$ 10 ng/mL. If iPSA concentration was $>$ 30 ng/mL, patients were excluded. Patients were eligible to participate if they had at least one tumor lesion visible on mpMRI. Patients with a medical contraindication to undergo MRI scanning or prostatic fiducial marker implantation were considered ineligible. Furthermore, patients were excluded if they had undergone prior pelvic radiotherapy or a prior transurethral resection of the prostate (TURP); or if they had severe lower urinary tract symptoms defined by an International Prostate Symptom Score (IPSS) of 15 or more. Patients needed to provide written informed consent before enrolment.

Procedures

All patients underwent a radiotherapy planning CT and mpMRI scan, which were co-registered for delineation purposes. The radiotherapy planning CT and all treatment sessions were performed with a comfortably filled bladder. At one out of the four participating centers (RadboudUMC) a rectal balloon was used. The radiotherapy planning mpMRI exam consisted of several sequences including T2-weighted, dynamic contrast-enhanced, and diffusion-weighted MRI. Before performing the radiotherapy planning CT scan, three to four prostatic fiducial markers were placed in all participants by a transperineal or transrectal approach for target positioning. Androgen deprivation therapy (ADT) was prescribed at the discretion of the treating radiation oncologist with no specific treatment intervention required by the trial protocol.

The prostate clinical target volume (CTV) comprised the whole prostate gland including a 4 mm margin around the gross tumor volume (GTV) for microscopic extracapsular extension, excluding the surrounding organs at risk (OARs). Visible tumor lesions on mpMRI were contoured as GTV in collaboration with an experienced uroradiologist. The seminal vesicles were contoured up to the radiation oncologist's discretion. In case of seminal vesicle invasion, the entire seminal vesicles were included by all radiation oncologists. The planning target volume (PTV) was created by adding an isotropic margin of 4–5 mm to the CTV. The rectum, anal canal, bladder, urethra, small bowel, penile bulb and femoral heads were delineated as OARs. A 2 mm isotropic planning risk volume (PRV) margin was generated for both the rectum and urethra. All patients were aimed to be treated with an SBRT plan delivering 35 Gy to the whole prostate gland in 5 weekly fractions with a simultaneous integrated iso-toxic focal boost up to 50 Gy to the GTV. The volume of the CTV receiving at least the prescribed dose of 35 Gy (V35) needed to be at least 99 %. The prescription dose to the prostate PTV was 33.25 Gy (95 % of 35 Gy), and the prescription dose to the GTV was an iso-toxic boost up to 50 Gy. The focal boost dose was escalated as high as achievable while maintaining the OAR dose constraints. No limit on target dose heterogeneity was specified by the protocol, but effort was made to limit the maximum dose (D0.1 cc) to $\leq$ 52 Gy. The detailed planning objectives are summarized in eTable 1. Treatment planning software was used to create VMAT plans with photon energies $\geq$ 6 MV. All patients were treated on C-arm linear accelerators. Daily on-line position verification of the prostate was performed either by orthogonal on-board kV X-ray imaging or CBCT.

Outcomes

The primary endpoint on feasibility and acute toxicity has been previously reported [21]. In the current analysis, prespecified secondary endpoints on bDFS, late toxicity and HRQoL were analysed. Biochemical failure was defined by the Phoenix consensus definition as an increase in serum PSA of at least 2 ng/mL above the nadir value [22]. Additionally, to prevent patients with a benign PSA bounce after SBRT being incorrectly classified as PSA failures, PSA failure required consecutive rises in PSA without a spontaneous decrease to the pre-bounce level or lower [23]. Late toxicity was defined as toxicity occurring at least 90 days after the first radiation treatment. Clinician-reported outcomes were measured using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). Patient-reported outcomes were collected using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and the prostate-specific EORTC QLQ-PR25 questionnaire. Participants were assessed at baseline, during the acute toxicity period, and then once every 6 months for the first year and once every year up to year five.

Statistical analysis

The sample size of 100 patients was calculated, based on the primary endpoint, to achieve a power of 82 % with a one-sided significance level of 0.05 to detect a $\geq$ 6 % increase of the acute toxicity incidence grade $\geq$ 3 compared to the acute toxicity percentages reported during and after

conventional EBRT [21]. All analyses were performed in the as-treated population with patients included if they received at least 1 radiotherapy session. Descriptive analysis was conducted for all patients with medians, IQRs, and ranges calculated for continuous variables and proportions calculated for categorical variables. The Kaplan-Meier method was used to perform time-to-event analyses. Data for patients were censored for the bDFS analysis at the date of death or time of last PSA assessment. We created a dose–response curve with the predicted probability of biochemical failure up to 7 years as a function of the near minimum dose (D_{99}) to the intraprostatic lesion using logistic regression.

The frequency and percentage of each toxicity grade was assessed at each timepoint for genitourinary toxicity, gastrointestinal toxicity and sexual function. Patient-reported HRQoL outcome scores were calculated for the urinary (Q31-Q37; Q39), bowel (Q40-Q43) and sexual activity (Q50-Q51) subdomains based on the EORTC QLQ-C30 and EORTC QLQ-PR25 questionnaires. All HRQoL scores were calculated in accordance with the EORTC QLQ scoring manual, converted to 0–100 scales and, if necessary, reversed so that 100 represents good HRQoL, high functionality and low symptom complaint. Linear mixed models were used to assess changes in HRQoL outcomes over time. A p-value $<$ 0.05 was considered statistically significant, using Bonferroni correction. Changes in HRQoL score from baseline to follow-up were defined as little (≈5-10), moderate (≈10-20) and significant (>20) minimally clinically important change (MCIC) at individual patient level [24,25]. All data were analysed using SPSS, version 29.0.1 (IBM Corp., Armonk, NY, USA).

Results

Between April 2016 and December 2018, 100 men were enrolled and treated in the hypo-FLAME trial. Patient demographics and treatment characteristics are outlined in Table 1. The median age at time of first treatment was 73 years (range, 57–84 years). Of note, 75 % of the patients were classified as high-risk PCa patients according to the EAU risk classification [26]. Hormone therapy was prescribed to most patients (62 %). The median near minimum dose received by 99 % of the GTV volume (D_{99}) was 40.3 Gy (range, 36.2–50.7 Gy), with a median mean dose (D_{mean}) to the GTV of 44.7 Gy (range, 37.7–50.9 Gy). Detailed dose statistics for each structure are summarized in eTable 2.

Table 1
Patient demographics, clinical characteristics and treatment details.

Characteristic	Total study cohort, No. (%) (n = 100)
Age, median (range), year	73 (57 – 84)
EAU risk group	
Intermediate	25
High	75
NCCN risk group	
Favorable intermediate	11
Unfavorable intermediate	21
High	45
Very high	23
Initial PSA, median (range), ng/mL	10.8 (3.0 – 29.0)
AJCC 7th edition clinical tumor stage	
T1c	3
T2a	25
T2b	11
T2c	14
T3a	44
T3b	3
ISUP grade group	
1	18
2	33
3	24
4	15
5	10
Intended androgen deprivation therapy	
LHRH agonists/antagonists	59
Antiandrogens	3
None	38
Intended androgen deprivation therapy duration	
None	38
Short term (≤ 6 months)	31
Long term (6 – 36 months)	31

At the time of analysis, all patients had a potential follow-up of 5 years and median follow-up was 61 months. At 5-year follow-up, six patients had evidence of biochemical failure, resulting in an actuarial 5-year bDFS of 93 % (95 % CI, 86 % to 97 %) (Fig. 1). All patients with biochemical failure underwent prostate-specific membrane antigen positron emission tomography (PSMA PET) imaging. Out of the six relapsed patients, one patient, in whom GTV D_{99} reached 39.9 Gy, had a local recurrence in combination with distant metastatic disease, two patients failed in the pelvic lymph nodes without local recurrence and three patients had distant metastatic disease without local failure. For two additional patients, biochemical failure was reported after more than 5 year follow-up. Furthermore, for two patients, the PSA value reached the criteria for biochemical failure with a subsequent spontaneous decrease below these criteria. Both were classified as a benign PSA bounce. The biochemical failure rate up to 7 years is shown as a function of the achieved D_{99} to the GTV (Fig. 2). Six patients died up to 5 years after treatment of whom none due to PCa, resulting in a 5-year overall survival of 94 % (95 % CI, 87 % to 97 %).

At 5 years, 12 % of the patients had CTCAE grade 2 or worse genitourinary toxicity and cumulative incidence rates of late CTCAE grade 2 or worse genitourinary toxicity were 28 % (Fig. 3). The most frequently reported CTCAE grade 2 or worse late toxicity was urinary frequency, which peaked at 6 months, with 14 % of the patients reporting grade 2 urinary frequency. The cumulative incidence rate of late grade 3 genitourinary toxicity was 2 %. According to the CTCAE criteria, 4 % of the patients had grade 2 or worse gastrointestinal toxicity at 5 years and cumulative incidence rates of late grade 2 or worse gastrointestinal toxicity were 14 % (Fig. 3). The cumulative incidence rate of late grade 3 gastrointestinal toxicity was 1 %. Neither CTCAE grade 4 or 5 genitourinary nor gastrointestinal toxicity was reported up to 5 years after treatment. The prevalence of CTCAE grade 2 or worse erectile dysfunction at 5 years was 45 % with a baseline prevalence of 20 %. The cumulative incidence of late CTCAE grade 2 or worse erectile dysfunction in the patients treated without ADT (n = 38) was 58 % with a baseline prevalence of 6 %.

Based on the observed data at 5 years, 24 %, 12 % and 24 % of the patients experienced a moderate or significant MCIC in urinary, bowel function and sexual activity HRQoL, respectively (Fig. 4). The mean

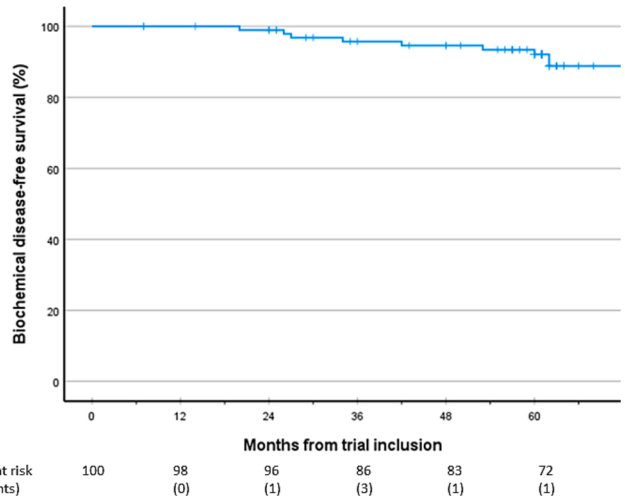

Fig. 1. .

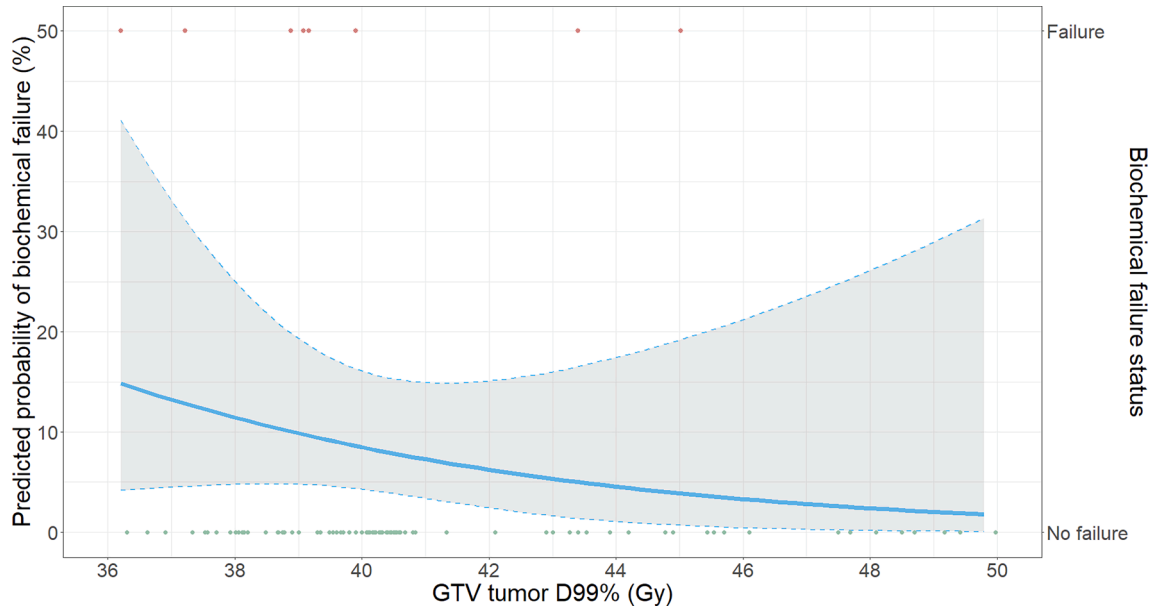

Fig. 2. .

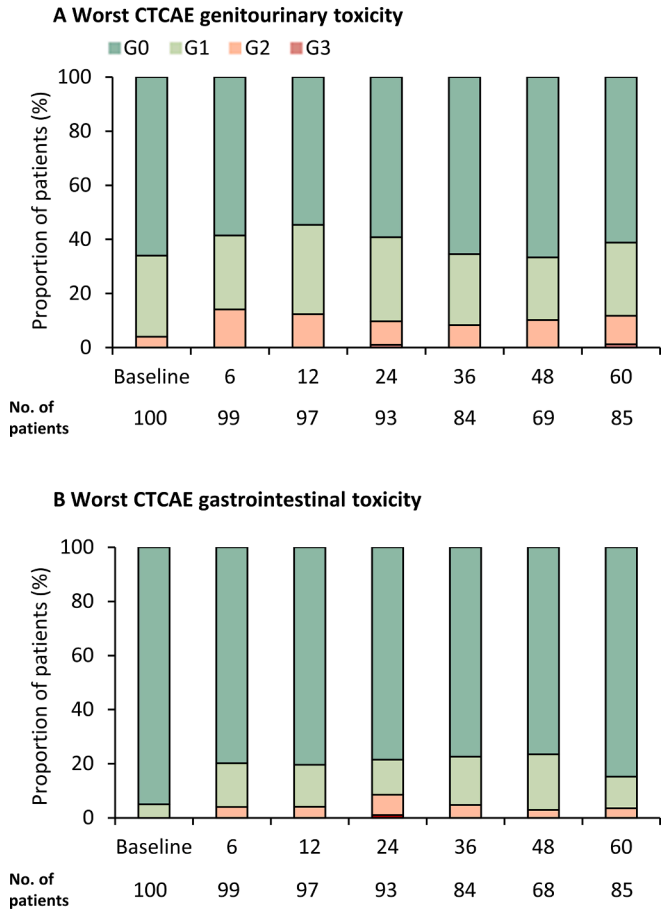

Fig. 3. .

HRQoL score due to urinary bother was back to baseline after 6 months. There was a significant difference between the bowel function HRQoL mean score at baseline compared with 5 years after treatment ($p = 0.014$). There was no significant difference between the sexual activity mean score at baseline compared to the 5-year value.

Discussion

In this 5-year analysis of the hypo-FLAME trial, the efficacy and late clinician- and patient-reported side effects of focal boosted SBRT for intermediate- and high-risk PCa were evaluated. In contrast to most previous ultra-hypofractionation trials, the hypo-FLAME trial was heavily weighted towards high-risk patients (75 %). When comparing the reported 5-year outcomes of focal boosted SBRT for patients with mainly high-risk PCa with the results of the PACE-B trial, delivering whole gland SBRT to patients with mainly intermediate risk PCa, the observed bDFS of 93 % in the hypo-FLAME trial approximates the 5-year bDFS of 95.7 % reported in the PACE-B trial [11]. Until now, only a limited number of other SBRT studies that included patients with high-risk PCa reported 5-year biochemical control rates ranging from 81 % to 85 % [27–29].

When comparing the treatment administered in the hypo-FLAME trial with that in the PACE-B trial, some differences can be noted. First, a considerable proportion of patients in the hypo-FLAME trial were concomitantly treated by hormonal therapy. A synergistic effect between hormonal treatment and radiotherapy may be responsible for approaching the 5-year oncological outcome rates of the ultra-hypofractionation arm of the PACE-B trial in a substantially higher-risk population. A second possible reason for approaching the excellent outcome of the PACE-B results in the hypo-FLAME trial is the higher dose administered to the macroscopic intraprostatic tumor. The patterns of failure analysis of the FLAME trial showed a dose–response relationship, whereby an increase in focal boost dose was associated with improved local, regional and distant metastatic disease control in predominantly high-risk PCa [30,31]. In the hypo-FLAME trial, administration of a simultaneous integrated iso-toxic focal boost up to 50 Gy was aimed for, with final achievement of median D_{99} of 40.3 Gy and a D_{mean} of 44.7 Gy delivered to the GTV, compared to the aim of the PACE-B trial to deliver at least 40 Gy to 95 % of the whole gland CTV. This focal dose escalation also seems to be a possible explanation for the higher bDFS found in the hypo-FLAME trial compared, although not randomized, to the previous studies in patients with high-risk PCa, delivering doses ranging from 35 Gy to 40 Gy to the whole prostate gland [28,29]. Furthermore, the 5-year bDFS outcome results of the hypo-FLAME trial are in line with the 92 % in the focal boost arm of the conventionally fractionated phase III FLAME trial. In line with the FLAME trial outcomes, the dose–response relation for biochemical failure seems to

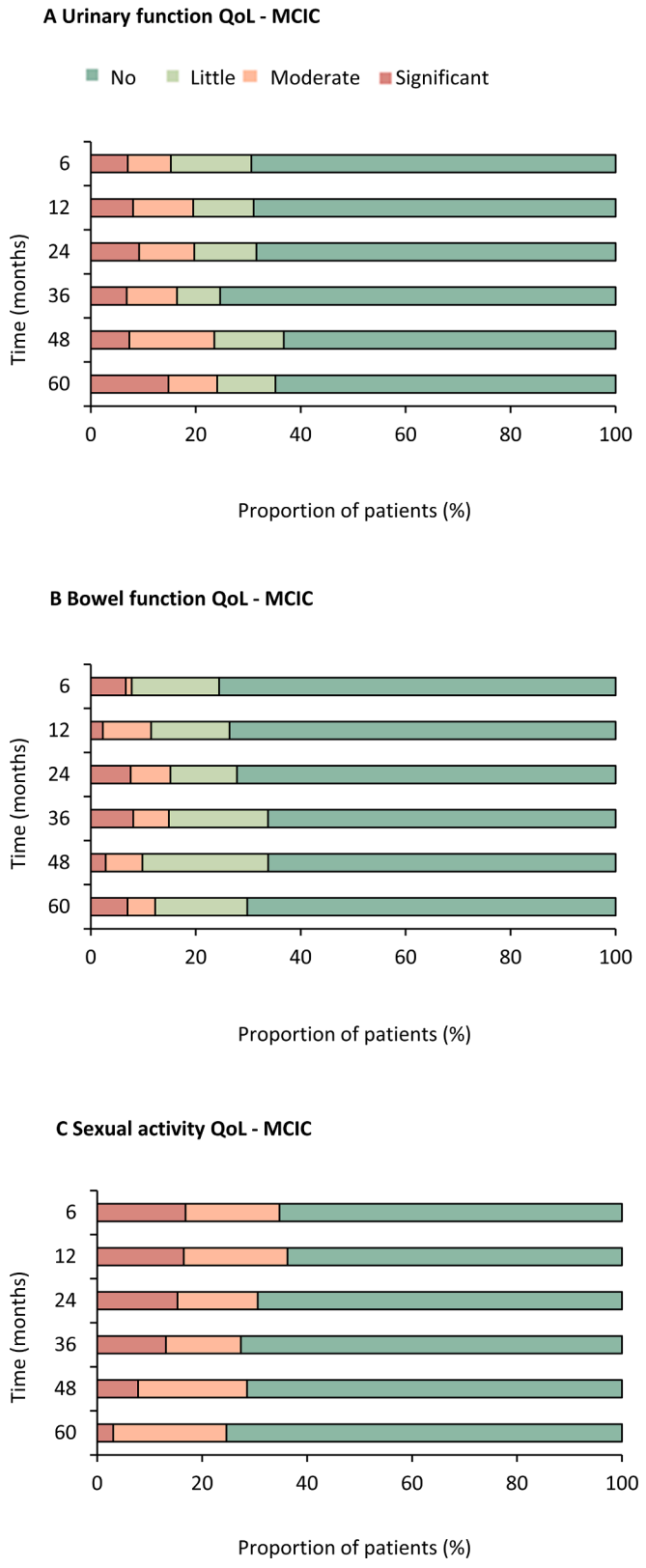

Fig. 4. .

decrease with increasing near minimum GTV dose.

Focussing on the long term safety and tolerability of the hypo-FLAME strategy, similar long term clinician- and patient-reported toxicity rates were found compared to other non-boost ultra-hypofractionation trials. The reported CTCAE grade 2 or worse genitourinary and gastrointestinal toxicity rates at 5 year were slightly higher compared to the Radiation Therapy Oncology Group (RTOG) grade 2 or worse genitourinary and toxicity rates of around 5 % and 1 %, respectively, found by the non-boosted HYPO-RT-PC and PACE-B trials. However, when comparing the results of the hypo-FLAME trial with the non-boosted trials, we should consider the known 10 % underestimation of toxicity as measured by RTOG compared with CTCAE scoring [32,33]. The hypo-FLAME toxicity outcomes suggested that ultra-hypofractionated, iso-toxic focal dose escalation can be achieved without increasing late side effects. This was already demonstrated for both moderate hypofractionated and conventionally fractionated schedules by the DELINEATE and FLAME trial, respectively [20,34]. The observed difference between the bowel function HRQoL mean score at baseline compared with 5 years after treatment is in line with the HRQoL results of the ProtecT trial in which patients were treated with conventionally fractionated radiotherapy [35]. Considering the anorectal dose–effect relationship for late gastrointestinal toxicity, demonstrated in the FLAME trial, the adoption of technological innovations leading to lower anorectal doses is of interest for future improvement in late bowel function HRQoL [36].

A limitation of the current trial is its nonrandomized character. However, to our knowledge, to date the hypo-FLAME trial provides the best evidence supporting the tolerability and efficacy of focal boosted SBRT in intermediate- and high-risk PCa. Thereby, we need to emphasise that the included high-risk patients the trial are limited to men with clinical T3a and T3b tumors with less than 5 mm invasion in the seminal vesicles on mpMRI and patients with an iPSA concentration $\leq$ 30 ng/mL. So far, a few other phase I/II trials add to the evidence base for focal boosted SBRT in intermediate- and high-risk PCa [37–39]. Randomized validation is needed and currently ongoing with the phase III hypo-FLAME 3.0 (NCT05705921) and HypoFocal-SBRT (DRKS00022915) trial [40]. Another shortcoming, inherent to focal boosting, is the potential imperfection of GTV delineation and its' dose coverage. Nevertheless, despite the presence of these hardly avoidable imperfections, the phase III FLAME trial showed a clinical benefit of conventionally fractionated focal boosting [20,41,42]. Finally, the prescribed dose of 35 Gy to the non-intraprostatic tumor prostate is less than the currently minimum recommended prostate SBRT dose of 36.25 Gy in 5 fractions by the National Comprehensive Cancer Network (NCCN). Considering the excellent disease outcome results achieved in the hypo-FLAME trial, the slightly lower dose delivered to the whole prostate gland could potentially be seen as a step towards de-escalation in combination with focal boosting to maximize disease control while minimizing toxicity [43]. Further whole prostate gland dose de-escalation to 30 Gy in 5 fractions combined with a focal boost up to 45 Gy to the GTV with a 4 mm intraprostatic margin is currently under investigation in the phase II DESTINATION trial (NCT05709496).

In conclusion, five-fraction prostate SBRT with an iso-toxic focal boost to the mpMRI-defined macroscopic intraprostatic tumor demonstrated encouraging 5-year efficacy outcomes in patients with mainly high-risk PCa. Furthermore, focal boosted ultra-hypofractionation for PCa appears to be feasible with low rates of toxicity, comparable to moderate and conventionally fractionated radiotherapy schedules.

CRediT authorship contribution statement

Cédric Draulans: Writing – original draft, Formal analysis. **Karin Haustermans:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Floris J. Pos:** Writing – review & editing, Supervision, Conceptualization. **Uulke A. van der Heide:** Writing – review & editing, Supervision, Conceptualization. **Lisa De Cock:** Writing – original draft. **Jochem van der Voort van Zyp:** Supervision. **Hans De Boer:** Writing – review & editing, Supervision, Conceptualization. **Robert J. Smeenk:** Writing – review & editing, Supervision, Conceptualization. **Martina Kunze-Busch:** Writing – review & editing, Conceptualization. **Evelyn M. Monninkhof:** Writing – review & editing. **Robin De Roover:** Writing – review & editing. **Sofie Isebaert:** Writing –

review & editing. **Linda G.W. Kerkmeijer:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank Karolína Guricová (Department of Radiation Oncology, The Netherlands Cancer Institute (NKI-AVL), Amsterdam, the Netherlands) for her support in figure design. The research project was funded by Kom op tegen Kanker (Stand up to Cancer), the Flemish cancer society.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110568.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209–49. https://doi.org/10.3322/CAAC.21660.

[2] Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2016;17:1047–60. https://doi.org/10.1016/S1470-2045(16)30102-4.

[3] Incrocci L, Wortel RC, Alemayehu WG, Aluwini S, Schimmel E, Krol S, 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;17:1061–9. https://doi.org/10.1016/S1470-2045(16)30070-5.

[4] Catton CN, Lukka H, Julian JA, Gu C-S, Martin J, Supiot S, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. J Clin Oncol 2017;35:1884–90. https://doi.org/10.1200/JCO.2016.71.7397.

[5] Hickey BE, James ML, Daly T, Soh FY, Jeffery M. Hypofractionation for clinically localized prostate cancer. Cochrane Database Syst Rev 2019;9:CD011462. https://doi.org/10.1002/14651858.CD011462.pub2.

[6] Schaeffer EM, Srinivas S, Adra N, An Y, Barocas D, Bitting R, et al. Prostate Cancer, Version 4.2023, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2023;21:1067–96. https://doi.org/10.6004/jnccn.2023.0050.

[7] Shelan M, Aebersold DM, Albrecht C, Böhmer D, Flentje M, Ganswindt U, et al. Moderately hypofractionated radiotherapy as definitive treatment for localized prostate cancer: Pattern of practice in German-speaking countries : A survey of the Prostate Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO) and the Working Party on Radiation Oncology of the German Cancer Society (DKG-ARO). Strahlenther Onkol 2021;197:993–1000. https://doi.org/10.1007/S00066-021-01820-2.

[8] Jackson WC, Silva J, Hartman HE, Dess RT, Kishan AU, Beeler WH, et al. Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies. Int J Radiat Oncol Biol Phys 2019;104:778–89. https://doi.org/10.1016/j.ijrobp.2019.03.051.

[9] Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet 2019;394:385–95. https://doi.org/10.1016/S0140-6736(19)31131-6.

[10] Tree AC, Ostler P, van der Voet H, Chu W, Loblaw A, Ford D, et al. Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2022;23:1308–20. https://doi.org/10.1016/S1470-2045(22)00517-4.

[11] van As N, Tree A, Patel J, Ostler P, Van Der Voet H, Loblaw DA, et al. 5-Year Outcomes from PACE B: An International Phase III Randomized Controlled Trial Comparing Stereotactic Body Radiotherapy (SBRT) vs. Conventionally Fractionated or Moderately Hypo Fractionated External Beam Radiotherapy for Localized Prostate Cancer. Int J Radiat Oncol Biol Phys 2023;117:e2–3. https://doi.org/10.1016/j.ijrobp.2023.08.027.

[12] Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. Int J Radiat Oncol Biol Phys 2009;74:1405–18. https://doi.org/10.1016/j.ijrobp.2008.10.091.

[13] Pahlajani N, Ruth KJ, Buyyounouski MK, Chen DYT, Horwitz EM, Hanks GE, et al. Radiotherapy doses of 80 Gy and higher are associated with lower mortality in men with Gleason score 8 to 10 prostate cancer. Int J Radiat Oncol Biol Phys 2012;82:1949–56. https://doi.org/10.1016/j.ijrobp.2011.04.005.

[14] Zelefsky MJ, Pei X, Chou JF, Schechter M, Kollmeier M, Cox B, et al. Dose escalation for prostate cancer radiotherapy: predictors of long-term biochemical tumor control and distant metastases-free survival outcomes. Eur Urol 2011;60:1133–9. https://doi.org/10.1016/j.eururo.2011.08.029.

[15] Eade TN, Hanlon AL, Horwitz EM, Buyyounouski MK, Hanks GE, Pollack A. What dose of external-beam radiation is high enough for prostate cancer? Int J Radiat Oncol Biol Phys 2007;68:682–9. https://doi.org/10.1016/j.ijrobp.2007.01.008.

[16] Hennequin C, Sargos P, Roca L, Silva M, Latorzeff I, Peiffert D, et al. Long-term results of dose escalation (80 vs 70 Gy) combined with long-term androgen deprivation in high-risk prostate cancers: GETUG-AFU 18 randomized trial. J Clin Oncol 2024;42:LBA259. https://doi.org/10.1200/JCO.2024.42.4_suppl.LBA259.

[17] Beckendorf V, Guerif S, Le Prisé E, Cosset JM, Bougnoux A, Chauvet B, 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;80:1056–63. https://doi.org/10.1016/j.ijrobp.2010.03.049.

[18] Cellini N, Morganti AG, Mattiucci GC, Valentini V, Leone M, Luzi S, et al. Analysis of intraprostatic failures in patients treated with hormonal therapy and radiotherapy: implications for conformal therapy planning. Int J Radiat Oncol Biol Phys 2002;53:595–9. https://doi.org/10.1016/S0360-3016(02)02795-5.

[19] Arrayeh E, Westphalen AC, Kurhanewicz J, Roach M, Jung AJ, Carroll PR, et al. Does local recurrence of prostate cancer after radiation therapy occur at the site of primary tumor? Results of a longitudinal MRI and MRSI study. Int J Radiat Oncol Biol Phys 2012;82. https://doi.org/10.1016/j.ijrobp.2011.11.030.

[20] Kerkmeijer L, Groen V, Pos F, Haustermans K, Monninkhof E, Smeenk R, 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 2021;39:787–96. https://doi.org/10.1200/JCO.20.02873.

[21] Draulans C, Van Der HUA, Haustermans K, Pos FJ, Van Der VJ, Zyp V, et al. Primary endpoint analysis of the multicentre phase II hypo-FLAME trial for intermediate and high risk prostate cancer. Radiother Oncol 2020;147:92–8. https://doi.org/10.1016/j.radonc.2020.03.015.

[22] Roach M, Hanks G, Thames H, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965–74. https://doi.org/10.1016/j.ijrobp.2006.04.029.

[23] Roy S, Loblaw A, Cheung P, Chu W, Chung HT, Vesprini D, et al. Prostate-specific antigen bounce after stereotactic body radiotherapy for prostate cancer: a pooled analysis of four prospective trials. Clin Oncol 2019;31:621–9. https://doi.org/10.1016/J.CLON.2019.05.001.

[24] Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139–44. https://doi.org/10.1200/JCO.1998.16.1.139.

[25] Musoro JZ, Coens C, Sprangers MAG, Brandberg Y, Groenvold M, Flechtner HH, et al. Minimally important differences for interpreting EORTC QLQ-C30 change scores over time: A synthesis across 21 clinical trials involving nine different cancer types. Eur J Cancer 2023;188:171–82. https://doi.org/10.1016/j.ejca.2023.04.027.

[26] Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol 2021;79:243–62. https://doi.org/10.1016/j.eururo.2020.09.042.

[27] Foerster R, Zwahlen DR, Buchali A, Tang H, Schroeder C, Windisch P, et al. Stereotactic body radiotherapy for high-risk prostate cancer: a systematic review. Cancers (Basel) 2021;13:1–17. https://doi.org/10.3390/cancers13040759.

[28] Alayed Y, Cheung P, Vesprini D, Liu S, Chu W, Chung H, et al. SABR in High-Risk Prostate Cancer: Outcomes From 2 Prospective Clinical Trials With and Without Elective Nodal Irradiation. Int J Radiat Oncol Biol Phys 2019;104:36–41. https://doi.org/10.1016/j.ijrobp.2018.11.011.

[29] King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, et al. Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiother Oncol 2013;109:217–21. https://doi.org/10.1016/j.radonc.2013.08.030.

[30] Groen VH, Haustermans K, Pos FJ, Draulans C, Isebaert S, Monninkhof EM, et al. Patterns of Failure Following External Beam Radiotherapy With or Without an Additional Focal Boost in the Randomized Controlled FLAME Trial for Localized Prostate Cancer. Eur Urol 2022;82:252–7. https://doi.org/10.1016/j.eururo.2021.12.012.

[31] Guricová K, van der Heide UA, Kerkmeijer LGW, Pos F, Monninkhof E, Haustermans K. Who needs a mean dose if you can FLAME? Radiother Oncol 2022;174:171–2. https://doi.org/10.1016/j.radonc.2022.06.020.

[32] Fonteyne V, Villeirs G, Lumen N, De Meerleer G. Urinary toxicity after high dose intensity modulated radiotherapy as primary therapy for prostate cancer. Radiother Oncol 2009;92:42–7. https://doi.org/10.1016/j.radonc.2009.03.013.

[33] David R, Buckby A, Kahokehr AA, Lee J, Watson DI, Leung J, et al. Long term genitourinary toxicity following curative intent intensity-modulated radiotherapy for prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2023;26:8–15. https://doi.org/10.1038/S41391-022-00520-X.

[34] Tree AC, Satchwell L, Alexander E, Blasiak-Wal I, deSouza NM, Gao A, et al. Standard and Hypofractionated Dose Escalation to Intraprostatic Tumor Nodules in

Localized Prostate Cancer: 5-Year Efficacy and Toxicity in the DELINEATE Trial. Int J Radiat Oncol Biol Phys 2023;115:305–16. https://doi.org/10.1016/j.ijrobp.2022.09.058.

[35] Lane JA, Donovan JL, Young GJ, Davis M, Walsh EI, Avery KNL, et al. Functional and quality of life outcomes of localised prostate cancer treatments (Prostate Testing for Cancer and Treatment [ProtecT] study). BJU Int 2022;130:370–80. https://doi.org/10.1111/BJU.15739.

[36] Groen VH, Zuithoff NPA, van Schie M, Monninkhof EM, Kunze-Busch M, de Boer HCJ, et al. Anorectal dose-effect relations for late gastrointestinal toxicity following external beam radiotherapy for prostate cancer in the FLAME trial. Radiother Oncol 2021;162:98–104. https://doi.org/10.1016/j.radonc.2021.06.033.

[37] Yasar B, Suh Y-E, Chapman E, Nicholls L, Henderson D, Jones C, et al. Simultaneous Focal Boost With Stereotactic Radiation Therapy for Localized Intermediate- to High-Risk Prostate Cancer: Primary Outcomes of the SPARC Phase 2 Trial. Int J Radiat Oncol Biol Phys 2024. https://doi.org/10.1016/j.ijrobp.2024.03.009.

[38] Cloitre M, Valerio M, Mampuya A, Rakauskas A, Berthold D, Tawadros T, et al. Toxicity, quality of life, and PSA control after 50 Gy stereotactic body radiation therapy to the dominant intraprostatic nodule with the use of a rectal spacer: results of a phase I/II study. Br J Radiol 2023;96. https://doi.org/10.1259/bjr.20220803.

[39] Dornisch AM, Zhong AY, Poon DMC, Tree AC, Seibert TM. Focal radiotherapy boost to MR-visible tumor for prostate cancer: a systematic review. World J Urol 2024;42. https://doi.org/10.1007/S00345-023-04745-W.

[40] Zamboglou C, Spohn SKB, Adebahr S, Huber M, Kirste S, Sprave T, et al. PSMA-PET/MRI-Based Focal Dose Escalation in Patients with Primary Prostate Cancer Treated with Stereotactic Body Radiation Therapy (HypoFocal-SBRT): Study Protocol of a Randomized, Multicentric Phase III Trial. Cancers (Basel) 2021;13. https://doi.org/10.3390/cancers13225795.

[41] van Schie MA, Dinh CV, van Houdt PJ, Pos FJ, Heijmink SWTJP, Kerkmeijer LGW, et al. Contouring of prostate tumors on multiparametric MRI: evaluation of clinical delineations in a multicenter radiotherapy trial. Radiother Oncol 2018;128:321–6. https://doi.org/10.1016/j.radonc.2018.04.015.

[42] van Schie MA, Janssen TM, Eekhout D, Walraven I, Pos FJ, de Ruiter P, et al. Knowledge-Based Assessment of Focal Dose Escalation Treatment Plans in Prostate Cancer. Int J Radiat Oncol Biol Phys 2020;108:1055–62. https://doi.org/10.1016/j.ijrobp.2020.06.072.

[43] Le Guevelou J, Bosetti DG, Castronovo F, Angrisani A, de Crevoisier R, Zilli T. State of the art and future challenges of urethra-sparing stereotactic body radiotherapy for prostate cancer: a systematic review of literature. World J Urol 2023;41:3287–99. https://doi.org/10.1007/S00345-023-04579-6.