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Published in	Journal of clinical oncology : official journal of the American Society of Clinical Oncology
Publication Date	2025-10
Link	https://dspace.library.uu.nl/handle/1874/467142
Citation	Menne Guricová, K, Draulans, C, Pos, F J, Kerkmeijer, L G W, Monninkhof, E M, Smeenk, R J, Kunze-Busch, M, de Boer, H C J, van der Voort van der Zyp, J R N, Haustermans, K & van der Heide, U A 2025, 'Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer : 10-Year Outcomes of the FLAME Trial', Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 43, no. 28, pp. 3065-3069. https://doi.org/10.1200/JCO-25-00274
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Universitair Medisch Centrum Utrecht (UMCU)	Yes

Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: 10-Year Outcomes of the FLAME Trial

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DOI <https://doi.org/10.1200/JCO-25-00274>

ABSTRACT

The FLAME trial hypothesized that focal boosting of intraprostatic tumor lesion(s) in addition to standard external beam radiotherapy (EBRT) improves biochemical disease-free survival (bDFS). In this multicenter randomized phase III trial, patients with intermediate- and high-risk prostate cancer (PCa) were assigned to the standard (EBRT of 77 Gy in 35 fractions to the whole prostate gland) or focal boost arm (standard EBRT with a focal boost of up to 95 Gy to magnetic resonance imaging–visible lesion(s)). Initial 5-year results showed a significant improvement in the focal boost arm for bDFS without additional toxicity. Here, we report bDFS, disease-free survival (DFS), local DFS, regional lymph node DFS, distant metastasis-free survival (DMFS), and overall survival (OS) after a 10-year follow-up. Dose-response curves were created using the dose heterogeneity in the study arm. Between 2009 and 2015, 571 patients were randomly assigned. The 10-year bDFS was 71% in the standard arm versus 86% in the focal boost arm. A significant improvement was also observed for other end points, except DMFS and OS. However, the dose-response curve suggests an association between dose and distant metastatic failure. The 10-year results demonstrated the sustained benefit of focal boosting on bDFS. By preventing biochemical failure, men are spared the potential burden of PCa recurrence.

ACCOMPANYING CONTENT

- Appendix
- Data Sharing Statement
- Protocol

Accepted June 24, 2025

Published August 4, 2025

J Clin Oncol 43:3065-3069

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INTRODUCTION

External beam radiotherapy (EBRT) is one of the standard treatment modalities for patients with intermediate- or high-risk prostate cancer (PCa). Dose to the prostate gland in the radiotherapy treatment of localized PCa has been historically increasing to achieve an improved clinical outcome. However, whole-gland dose escalation above 80 Gy was not desirable because of unacceptable toxicities.¹ The Focal Lesion Ablative Microboost in prostate cancer (FLAME) trial hypothesized that dose escalation at the location of the primary tumor increases biochemical disease-free survival (bDFS).² The primary outcome analysis demonstrated that focal boosting indeed improves the 5-year bDFS to 92% compared with 85% in the standard arm without additional toxicity.³ Here, we report the results of the FLAME trial after a 10-year follow-up.

METHODS

Study Design and Patients

The FLAME trial is a multicenter, phase III, randomized controlled trial for patients with localized intermediate- and

high-risk PCa. Patients were randomly assigned in a 1:1 ratio between the standard arm (EBRT of 77 Gy in 35 fractions to the whole prostate gland) and the focal boost arm (EBRT with a simultaneously integrated focal boost of up to 95 Gy to the magnetic resonance imaging–visible lesion/lesions [gross tumor volume (GTV)]). The organ-at-risk constraints were prioritized over the focal boost dose. Further study details have been published previously.³ The study protocol was approved by the medical ethics committees of the University Medical Center Utrecht (NL26038.041.08) for the Netherlands and of the University Hospitals Leuven (B322201110225) for Belgium. Written informed consent was provided by all participating patients.

Outcomes

The key end point was 10-year bDFS. Further analyzed outcomes were 10-year disease-free survival (DFS), local DFS, regional lymph node DFS, distant metastasis-free survival (DMFS), and overall survival (OS). The detailed definition of these end points can be found in [Appendix 1](#) (online only). Using dose heterogeneity in the study arm, we created dose-response curves based on the near-minimum radiation dose to the GTV (D98%) using logistic regression. No additional

toxicity outcomes were collected after 60 months. The detailed statistical analysis is provided in [Appendix 1](#).

RESULTS

There were 571 patients recruited between 2009 and 2015, 287 in the standard arm and 284 in the focal boost arm ([Table 1](#)). Intention-to-treat analysis included 276 patients from the standard arm and 281 from the focal boost arm. The CONSORT diagram is shown in [Figure 1](#).

The median follow-up was 106 months. The 10-year bDFS was 71% (95% CI, 65% to 77%) in the standard arm versus 86% (95% CI, 81% to 91%) in the focal boost arm with a statistically significant difference between trial arms ($P < .001$; [Fig 2A](#)). The addition of a focal boost reduced the number of biochemical failures by more than half (adjusted hazard ratio [HR], 0.40 [95% CI, 0.26 to 0.61]; $P < .001$). The dose-response curve shows a strong association between dose and biochemical failure, suggesting a biochemical failure rate of about 5% for dose levels above 90 Gy ([Fig 2B](#)). Similarly, significant differences were found for DFS ($P < .001$, [Appendix Fig A1](#)), local DFS ($P < .01$, [Appendix Fig A2](#)), and regional lymph node DFS ($P < .01$, [Appendix Fig A3](#)). The 10-year results for DFS were 67% (95% CI, 61% to 73%) in the standard arm versus 81% (95% CI, 76% to 87%) in the focal boost arm (HR, 0.48 [95% CI, 0.33 to 0.69]; $P < .001$); the 10-year results for local DFS was 86% (95% CI, 81% to 91%) in the standard arm versus 95% (95% CI, 92% to 98%) in the focal boost arm; and the 10-year results for regional lymph node DFS was 85% (95% CI, 80% to 90%) in the standard arm versus 94% (95% CI, 90% to 97%) in the focal boost arm. There was no statistically significant difference for DMFS ($P = .17$, [Fig 3A](#)) and OS ($P = .77$). The 10-year results for DMFS were 83% (95% CI, 78% to 88%) in the standard arm versus 87% (95% CI, 83% to 92%) in the focal boost arm (HR, 0.69 [95% CI, 0.43 to 1.10]; $P = .12$). The dose-response curve for distant metastases suggests an association with dose, where a higher D98% is associated with lower rates of distant metastatic failure ([Fig 3B](#)). Unadjusted HRs can be found in [Appendix 1](#). Competing risk analysis results led to comparable conclusions as the results of regular Cox regression. The results of the per-protocol analyses did not differ from the intention-to-treat results.

DISCUSSION

The FLAME trial demonstrated that the addition of an isotoxic focal boost to the standard treatment significantly improves bDFS, DFS, local DFS, and regional lymph node DFS. For the last, the 9% improvement at 10 years in the focal boost arm suggests that focal boosting can reduce regional failures without pelvic irradiation. The Kaplan-Meier analysis did not reveal a statistically significant difference between the trial arms for DMFS and OS although for the DMFS, the dose-response curve suggests a possible association

TABLE 1. Patient Characteristics of the Trial Population

Baseline Characteristic	Standard Arm (n = 287)	Focal Boost Arm (n = 284)
Age, years (mean)	70 (7)	70 (6)
Center		
UMCU, No. (%)	160 (56)	160 (56)
NKI, No. (%)	55 (19)	54 (19)
University Hospitals Leuven, No. (%)	47 (16)	46 (16)
Radboudumc, No. (%)	25 (9)	24 (9)
Initial PSA, ng/mL (standard deviation)	15.2 (14.9)	16.3 (13.9)
ISUP GG, No. (%)		
ISUP GG 1	55 (19)	47 (17)
ISUP GG 2 or 3	139 (48)	139 (49)
ISUP GG 4 or 5	93 (32)	98 (35)
Clinical T-stage, No. (%)		
T1c	27 (9)	23 (8)
T2a	29 (10)	28 (10)
T2b	18 (6)	19 (7)
T2c	35 (12)	42 (15)
T3a	124 (43)	111 (39)
T3b	45 (16)	57 (20)
T4	9 (3)	4 (1)
Risk stratification, No. (%)		
Low-risk	4 (1)	2 (1)
Intermediate-risk	43 (15)	43 (15)
High-risk	240 (84)	239 (84)
N-stage, No. (%)		
cN0	226 (79)	231 (81)
pN0<10 lymph nodes removed	48 (17)	33 (12)
pN0≥10 lymph nodes removed	13 (5)	20 (7)
Timing of hormonal therapy, No. (%)		
Neoadjuvant therapy	23 (8)	21 (7)
Duration of (neo-)adjuvant hormonal therapy received, months, No. (%)		
None	99 (35)	98 (35)
0-6	58 (20)	50 (18)
6-18	32 (11)	33 (12)
18-36	84 (29)	96 (34)
Missing	14 (5)	7 (3)
TURP, No. (%)		
Yes	41 (14)	36 (13)
No	246 (86)	248 (87)
Cardiovascular disease, No. (%)		
Yes	155 (54)	147 (52)
No	132 (46)	137 (48)
Diabetes mellitus, No. (%)		
Yes	31 (11)	30 (11)
No	256 (89)	254 (89)

NOTE. Continuous variables are presented as mean with standard deviation if normally distributed, otherwise as median with interquartile range.

Abbreviations: ISUP GG, International Society for Urological Pathology grade group; N, node; NKI, the Netherlands Cancer Institute; PSA, prostate-specific antigen; T, tumor; TURP, transurethral resection of the prostate; UMCU, University Medical Center Utrecht.

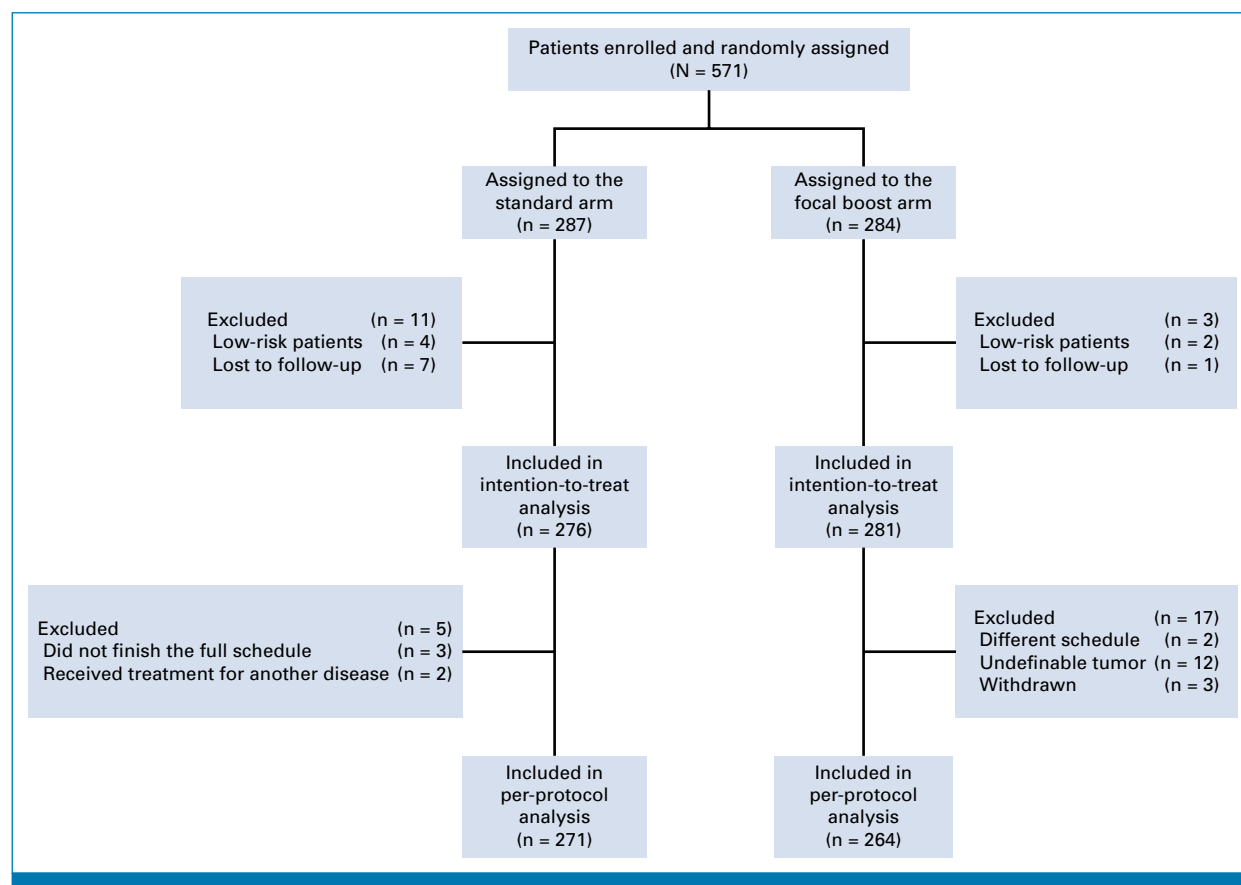


FIG 1. CONSORT diagram of the FLAME trial.

between dose and outcome. The current results corroborate the 5-year results, whereas the bDFS difference between arms increased from 7% to 15%.³ Despite no OS benefit, the positive effect of focal boosting on bDFS can be valuable for

patients. In comparison with other therapy options (eg, hormonal therapy, brachytherapy), there is no additional treatment-related toxicity, but 15% more men can be spared the potential burden of PCa recurrence.

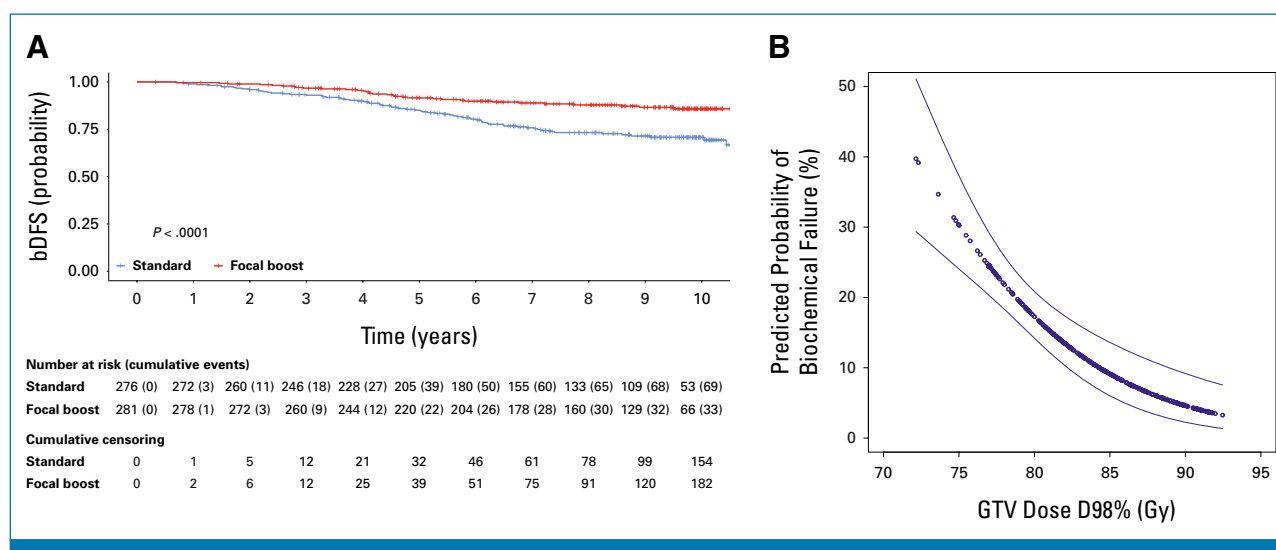


FIG 2. (A) Kaplan-Meier plot for bDFS and (B) the dose-response curve with predicted probability of biochemical failure. bDFS, biochemical disease-free survival; GTV, gross tumor volume.

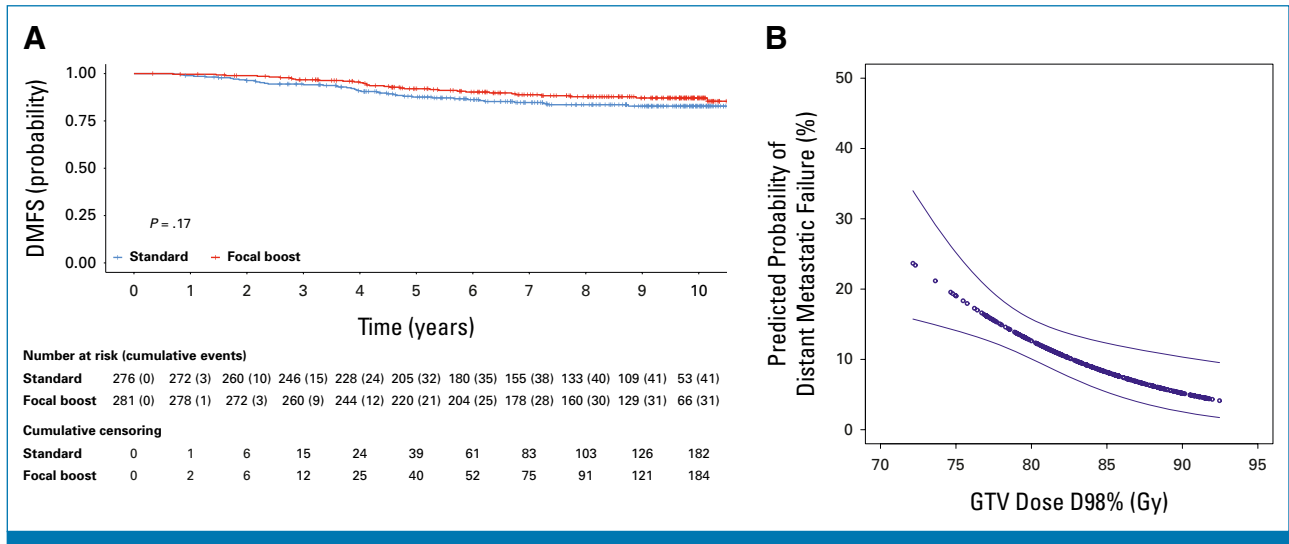


FIG 3. (A) Kaplan-Meier plot for DMFS and (B) the dose-response curve with predicted probability of distant metastatic failure. DMFS, distant metastasis-free survival.

The DMFS appeared to be a complex end point in the setting of this trial. At the trial start, prostate-specific membrane antigen-positron emission tomography was not available, and hence, some patients might have already been metastasized at the moment of inclusion. Moreover, consequential to the isotoxic boosting approach, almost half of the patients in the study arm did not receive a significantly high focal boost.⁴ The impact this might have had on the outcomes can be appraised through the dose-response curves. The heterogeneity of the focal boost dose might have weakened the benefit for DMFS more markedly because of the lower steepness of its dose-response curve.

Patients in the FLAME trial received androgen deprivation therapy (ADT) at the discretion of the treating physician with about one third of patients receiving no ADT at all although it was recommended as standard treatment. This might be due to the clinical practice in the Netherlands and Belgium where both doctors and their patients are more reluctant to the use of ADT because of its side effects. The characteristics of ADT were equally distributed between trial arms, meaning that the differences in outcomes between trial arms should be unaffected by it.

Because of the low α/β ratio of PCa, (ultra-)hypofractionation seems to be a promising strategy for delivering a

high dose. However, based on the meta-analysis by Vogelius and Bentzen, there might be a concern for achieving a high EQD2 with hypofractionation because of a possible increase in α/β ratio at high fraction doses.^{5,6} The ongoing hypo-FLAME 3.0 (ClinicalTrials.gov identifier: [NCT05705921](https://clinicaltrials.gov/ct2/show/study/NCT05705921)) and HypoFocal-SBRT (ClinicalTrials.gov identifier: [NCT06330909](https://clinicaltrials.gov/ct2/show/study/NCT06330909)) trials might provide more insights into the efficacy of hypofractionated schedules combined with focal boosting.⁷

The limitation of the current study is that it has not been powered for the additional analyzed outcomes. Moreover, at the start of the trial, there were no GTV contouring guidelines which might have led to an increased interobserver variability.⁸ Similarly, higher boost doses might have been achieved using improved treatment planning methods.⁴ Nonetheless, this variability may demonstrate the robustness of the focal boosting benefit since a significant difference was observed despite boost dose heterogeneity.

In conclusion, the 10-year report of the FLAME trial demonstrated the sustained benefit of focal boosting for patients with intermediate- and high-risk PCa on their bDFS. Furthermore, the dose-response curve for distant metastatic failure suggests a possible association between dose and this outcome.

AFFILIATIONS

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PRIOR PRESENTATION

Presented at the European Society for Radiotherapy and Oncology, Vienna, Austria, May 5, 2025.

SUPPORT

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

CLINICAL TRIAL INFORMATION

[NCT01168479](#) (FLAME)

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-25-00274>.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI <https://doi.org/10.1200/JCO-25-00274>.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: 10-Year Outcomes of the FLAME Trial**

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Karolína Menne Guricová**Employment:** HBox Therapies GmbH (I)**Leadership:** HBox Therapies GmbH (I)**Stock and Other Ownership Interests:** HBox Therapies GmbH (I)**Patents, Royalties, Other Intellectual Property:** HBox Therapies GmbH patents (I)**Floris J. Pos****Honoraria:** Amgen (Inst), Astellas Pharma (Inst)**Jochem R.N. van der Voort van der Zyp****Research Funding:** Philips Healthcare (Inst), Elekta (Inst)**Martina Kunze-Busch****Employment:** Elekta (I), Philips Healthcare (I)**Stock and Other Ownership Interests:** Philips Healthcare (I), Elekta (I)**Karin Haustermans****Honoraria:** Elsevier**Research Funding:** IBA**Uulke A. van der Heide****Research Funding:** Philips Healthcare (Inst), Elekta (Inst)

No other potential conflicts of interest were reported.

APPENDIX 1. SUPPLEMENTARY MATERIAL

End Point Definitions

Biochemical failure was defined according to the Phoenix criteria as a prostate-specific antigen (PSA) rise of 2 ng/mL over the PSA nadir value (the lowest PSA value after treatment). The additional end points, local disease-free survival (DFS), regional lymph node DFS, and distant metastasis-free survival (DMFS) were defined based on the corresponding failure location, with a recurrence in seminal vesicles being considered as a local failure. Disease-free survival was defined as being free from any type of failure (biochemical, clinical, and/or failure detected on imaging performed as a result of a clinical indication other than biochemical failure). With changing clinical practice over time, the type of imaging that was performed was done at the discretion of the treating physician. The imaging in patients with any type of failure included both conventional imaging (bone scintigraphy, computed tomography [CT], and magnetic resonance imaging) and positron emission tomography (PET) imaging (choline and prostate-specific membrane antigen [PSMA]). After 2018, PSMA-PET CT has become the standard method used for identification of the failure location and has also been used in the majority of failures in this cohort. Patients were censored at the last PSA follow-up, at the date of death, or at the moment of first failure.

Statistical Analysis

The FLAME trial was a superiority trial designed to detect an increase of 10% in the 5-year biochemical disease-free survival (bDFS) in the focal boost arm with a power of

80% and a significance level of 5% (one-sided). The 5-year bDFS of the standard arm was assumed to be 64%, which led to a sample estimate of 283 patients per arm.

Kaplan-Meier analysis using a log-rank test was used to assess the differences between trial arms for bDFS, DFS, local DFS, regional lymph node DFS, DMFS, and overall survival. We performed unadjusted and adjusted (center, age [years], initial PSA [ng/mL], T-stage, International Society for Urological Pathology grade group, duration of hormonal therapy [months], and timing of hormonal therapy [neoadjuvant or adjuvant]) Cox regression to derive the hazard ratio (HR) for bDFS, DFS, and DMFS. For adjusted Cox regression, a time-varying coefficient for the duration of hormonal therapy was considered, but Schoenfeld residual analysis did not show the need for this transformation for all bDFS, DFS, and DMFS ($P > .5$ for all). Competing risk analysis was performed with death from any cause as a competing risk using the Fine and Gray method. Primary analyses included the intention-to-treat population. We additionally performed per-protocol analyses. Patients excluded from per-protocol analysis received a different treatment schedule than intended. The analysis and figures were performed using R (v 4.3.1).

Estimated Unadjusted HRs

The unadjusted HRs for bDFS, DFS, and DMFS were 0.40 (95% CI, 0.27 to 0.61; $P < .001$), 0.49 (95% CI, 0.34 to 0.70; $P < .001$), and 0.72 (95% CI, 0.45 to 1.15; $P = .17$), respectively.

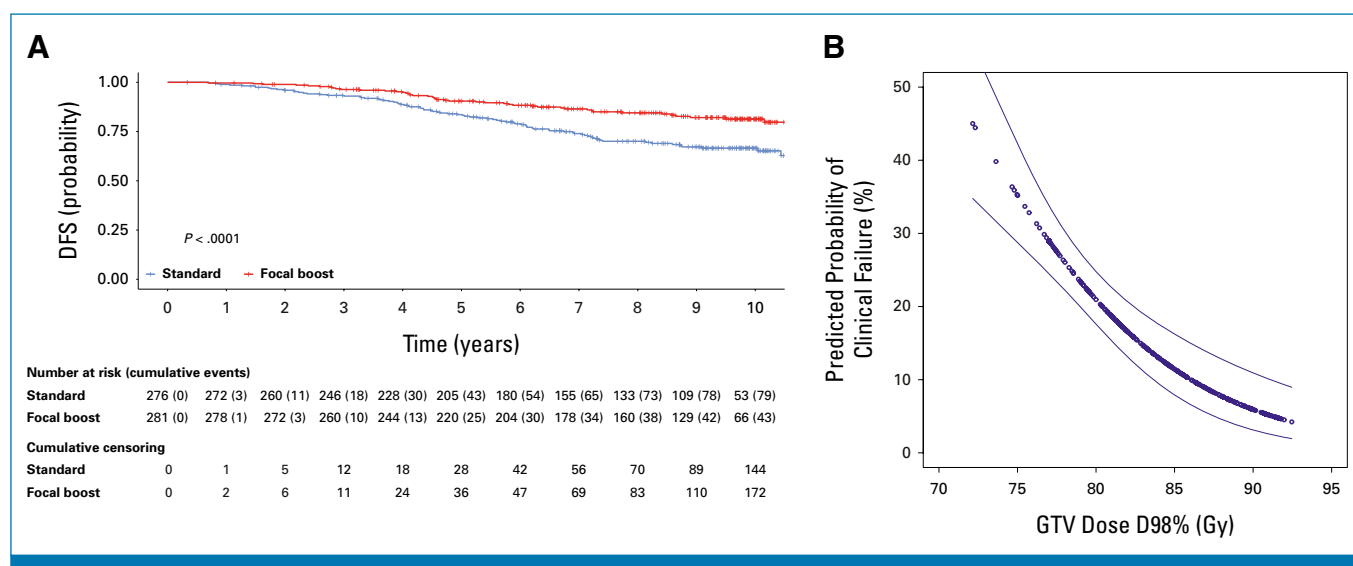


FIG A1. (A) Kaplan-Meier plot for DFS and (B) the dose-response curve with predicted probability of clinical failure. DFS, disease-free survival; GTV, gross tumor volume.

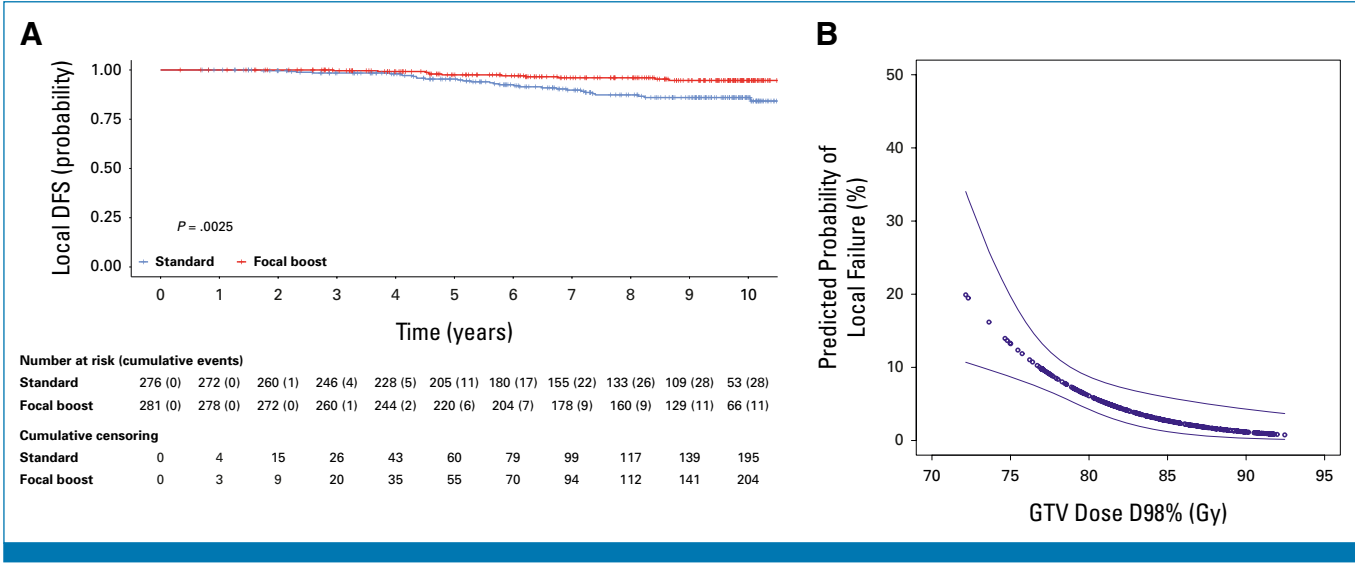


FIG A2. (A) Kaplan-Meier plot for local DFS and (B) the dose-response curve with predicted probability of local failure. DFS, disease-free survival; GTV, gross tumor volume.

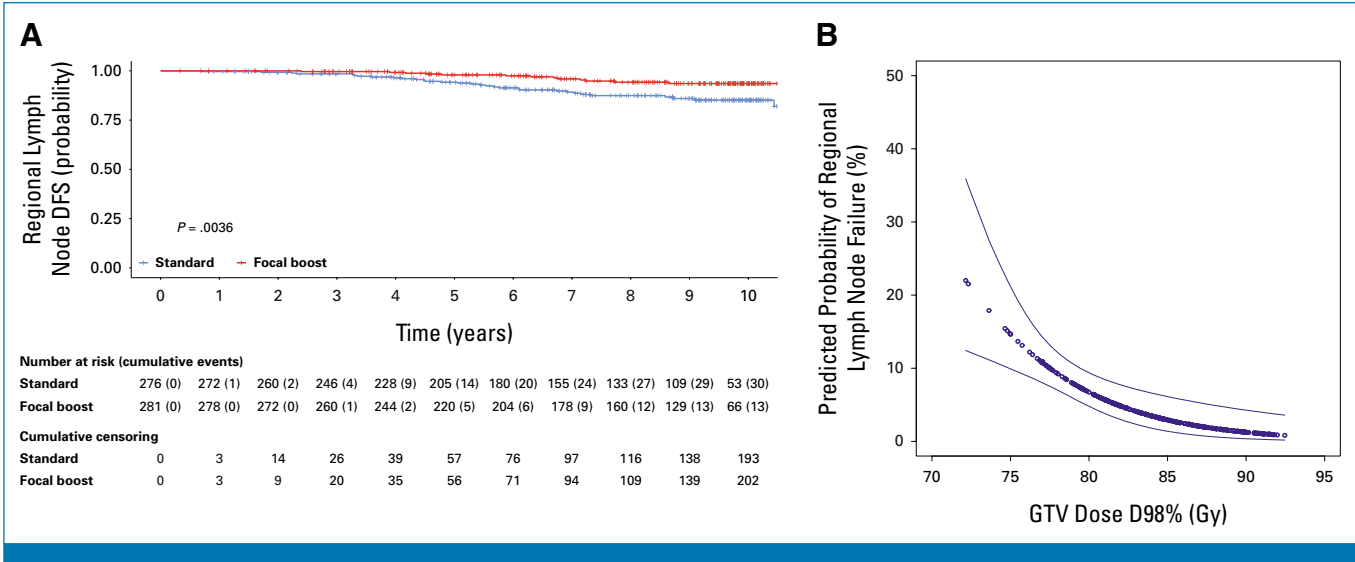


FIG A3. (A) Kaplan-Meier plot for regional lymph node DFS and (B) the dose-response curve with predicted probability of regional lymph node failure. DFS, disease-free survival; GTV, gross tumor volume.