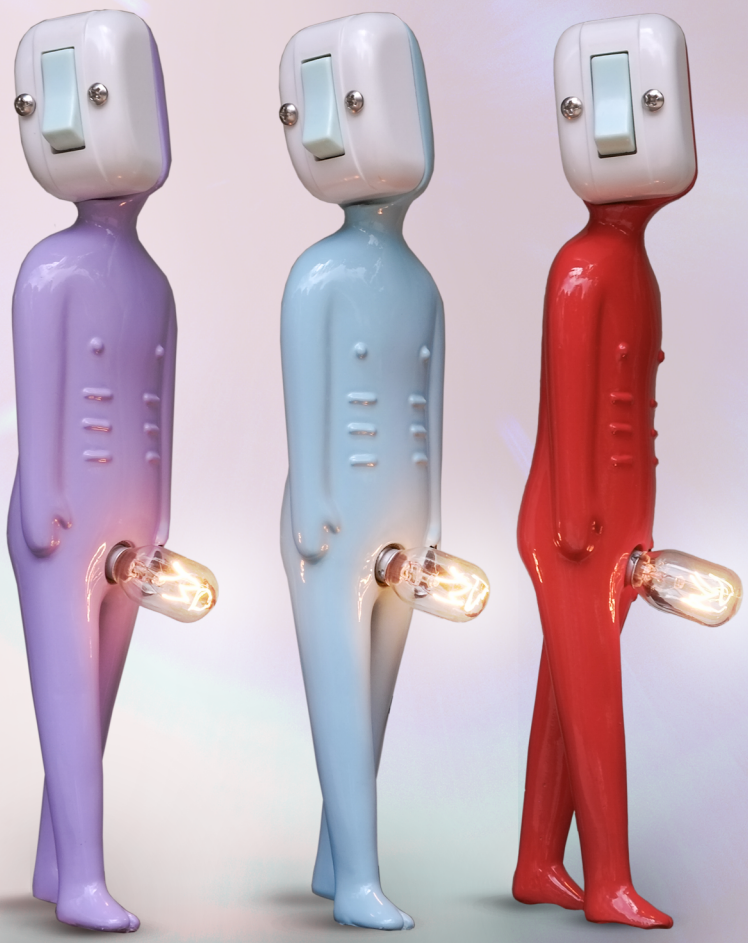
# TIME TO LIGHT THE FLAME

Focal boosting in external beam radiotherapy for localized prostate cancer



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Focal boosting in external beam radiotherapy for localized prostate cancer

Focale boost bij uitwendige bestraling voor gelokaliseerde prostaatkanker
*(met een samenvatting in het Nederlands)*

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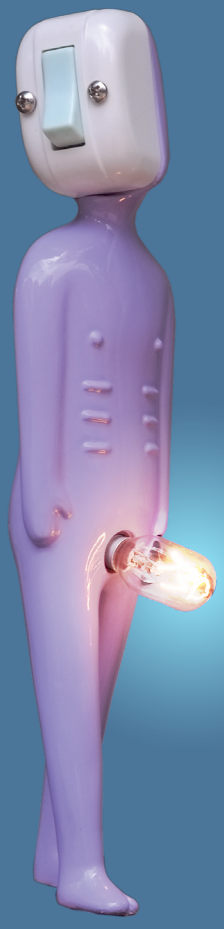


# General introduction

**Epidemiology**

From the 1990s, the incidence of prostate cancer increased in more developed regions, as a result of earlier detection of prostate cancer due to the introduction of blood sample screening on prostate specific antigen (PSA) (1). In 2018, approximately 1.28 million men worldwide were newly diagnosed with prostate cancer, with approximately 359.000 prostate cancer deaths that year (2). In developed countries, prostate cancer is the most common malignancy diagnosed in middle aged and older men. The lifetime risk of developing prostate cancer is estimated to be around 12.5% (3). Risk factors for the development of prostate cancer are age, race, family history, endogenous hormones, genetic polymorphism, and obesity (4). In 2020, prostate cancer was the most common diagnosed cancer in men aged ≥ 55 years in the Netherlands. The incidence of prostate cancer in the Netherlands was 11.1% (12.815 new diagnosis), with 3.003 prostate cancer deaths that year (5,6). Survival rates of prostate cancer are improving worldwide (4). In the Netherlands, the five-year survival rate of prostate cancer was 69.4% (68.4-70.5) between 1991 and 1995, compared to 89.1% (88.5-89.7) between 2011 and 2015 (6). As a result of population aging and growth, the estimated incidence of prostate cancer in the Netherlands is expected to increase up to 30-40% in 2040 (7).

**Diagnostics**

Symptoms attributable to prostate cancer occur late in the disease course and are often not prostate cancer specific. Lower urinary tract symptoms and haematuria might occur. A patient can also present with metastasis related symptoms such as bone pain. The first diagnostic step in men at risk of prostate cancer, or when either screening is indicated or requested by the patient, is digital rectal examination in combination with blood sample testing for PSA levels. Once prostate cancer is suspected after digital rectal examination and/or in case of elevated PSA levels, additional imaging for example Magnetic Resonance Imaging (MRI) and histopathological confirmation using prostate biopsies are required (8,9).

**Disease staging**

Once prostate cancer is confirmed, the disease stage is determined based on the Tumor Node Metastasis (TNM) classification (Table 1) (8,9). The T-stage describes the size and extent of the primary tumor, assessed with digital rectal examination (Table 1). The Gleason score describes the level of aggressiveness of the tumor and is determined based on glandular architecture and microscopic appearance based on tissue derived from prostate biopsies. The Gleason score results from adding the two most prevalent Gleason grades in the examined tissue. In 2014, another grading system, the International Society of Urological Pathology (ISUP) score was introduced, based on the Gleason score (Table 3) (8,9)

**Table 1.** 8th edition of the Union for International Cancer Control (UICC) clinical Tumor, Node, metastasis (TNM) classification(8,9)

| | | |
|---|---|---|
| **T - Primary Tumor (stage based on digital rectal examination only)** | | |
| TX | Primary tumor cannot be assessed | |
| T0 | No evidence of primary tumor | |
| T1 | Clinically inapparent tumor that is not palpable | |
| | T1a | Tumor incidental histological finding in 5% or less of tissue resected |
| | T1b | Tumor incidental histological finding in more than 5% of tissue resected |
| | T1c | Tumor identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA]) |
| T2 | Tumor that is palpable and confined within the prostate | |
| | T2a | Tumor involves one half of one lobe or less |
| | T2b | Tumor involves more than half of one lobe, but not both lobes |
| | T2c | Tumor involves both lobes |
| T3 | Tumor extends through the prostatic capsule | |
| | T3a | Extracapsular extension (unilateral or bilateral) |
| | T3b | Tumor invades seminal vesicle(s) |
| T4 | Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall | |
| **N - Regional (pelvic) Lymph Nodes[1]** | | |
| NX | Regional lymph nodes cannot be assessed | |
| N0 | No regional lymph node metastasis | |
| N1 | Regional lymph node metastasis | |
| **M - Distant Metastasis[2]** | | |
| M0 | No distant metastasis | |
| M1 | Distant metastasis | |
| | M1a Non-regional lymph node(s) | |
| | M1b Bone(s) | |
| | M1c Other site(s) | |

[1] Metastasis no larger than 0.2 cm can be designated pNmi.
[2] When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.

For treatment decision making purposes and to provide prognostic information, multiple risk classification scoring systems were developed over the years, including the D'Amico (10), National Comprehensive Cancer Network (NCCN) (11), European Association of Urology (EAU) (Table 2) (8,9) and the Cancer of the Prostate Risk Assessment (UCSF-CAPRA) (12). These risk classifications are based on the estimated risk of biochemical recurrence given certain clinical parameters. There are multiple definitions of biochemical recurrence, depending on the treatment modality. The cut-off value for biochemical recurrence following radical prostatectomy in the Netherlands is a postoperative PSA level of 0.2ng/mL. The lowest PSA value after treatment is called PSA nadir. Several definitions

of biochemical recurrence following radiotherapy exist. According to the frequently used Phoenix criteria, recurrence is defined as a PSA level of 2.0 ng/mL above PSA nadir (13). Localized disease is diagnosed in approximately 60% of the patients and is subdivided into low-, intermediate- and high-risk disease based on the previously mentioned risk classification systems. Parameters that are used are clinical T-stage, PSA level and Gleason score/ISUP score, for the UCSF-CAPRA score age is also included. At time of diagnosis, clinically advanced disease is observed in 20% and metastasized disease in 15% of patients (5).

**Table 2.** European Association of Urology (EAU) risk groups for biochemical recurrence of localized and locally advanced prostate cancer (8,9)

| **Definition** | | | |
|---|---|---|---|
| **Low-risk** | **Intermediate-risk** | **High-risk** | |
| PSA < 10 ng/mL | PSA 10-20 ng/mL | PSA > 20 ng/mL | any PSA |
| and GS < 7 (ISUP grade 1) | or GS 7 (ISUP grade 2/3) | or GS > 7 (ISUP grade 4/5) | any GS (any ISUP grade) |
| and cT1-2a | or cT2b | or cT2c | cT3-4 or cN+ |
| **Localized** | | | **Locally advanced** |

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

**Table 3.** International Society of Urological Pathology 2014 grade (group) system (8,9)

| **Gleason score** | **ISUP grade** |
|---|---|
| 2-6 | 1 |
| 7 (3+4) | 2 |
| 7 (4+3) | 3 |
| 8 (4+4 or 3+5 or 5+3) | 4 |
| 9-10 | 5 |

**The role of multiparametric MRI in screening and diagnostics of prostate cancer**

The use of MRI in prostate cancer screening was first described in 1980s and has evolved over time (14). Advanced MRI techniques with multiparametric MRI (mpMRI) and the development of guidelines for the reporting of prostate cancer lesions on MRI (15), allowed for mpMRI to play a role in the diagnosis and management of prostate cancer. The addition of functional (diffusion weighted (DWI) and dynamic contrast enhanced (DCE)) imaging to anatomical (T2 weighted) imaging, provides more accuracy in the detection of prostate cancer (16). The Prostate Imaging Reporting And Data System (PIRADS) score can be used to describe the level of suspicion of prostate cancer based on mpMRI visible lesions (15).

Current guidelines suggest using digital rectal examination to determine the clinical T-stage and use mpMRI findings as additional information for treatment planning (8,9). Ideally, mpMRI is carried out before prostate biopsies are performed in both the biopsy-naïve and repeated biopsy setting. In case of positive mpMRI, with a PIRADS score of three or higher, combined targeted and systematic biopsies should be performed to histopathologically confirm the presence of prostate cancer (8,9,17). The use of mpMRI-guided biopsies compared to TRUS-guided biopsies has led to a reduction in undersampling and understaging of clinically significant prostate cancer and at the same time to overdiagnosis, i.e., an increased detection of insignificant prostate cancer lesions (18–21). When using mpMRI in the prostate cancer work-up, prostate biopsies can be avoided in one in four men (21). In case of a clinically low suspicion of prostate cancer and a negative mpMRI, the treating physician may discuss to omit prostate biopsies with the patient (8,9). Avoiding unnecessary biopsies is likely to reduce health costs (22), the risk of overtreatment and biopsy related complications will be lower (23).

**Regional and distant metastatic staging in primary setting**

According to the EAU guidelines, in patients with unfavourable intermediate-risk and high-risk prostate cancer, an abdominal CT-scan and additional bone scintigraphy are performed to rule out metastatic disease. Research data suggest that Prostate Specific Membrane Antigen (PSMA) in Positron Emission Tomography (PET)-CT imaging in the primary setting for patients with high-risk prostate cancer, is more accurate when compared to the current standard consisting of CT imaging and bone scintigraphy (8,9). Although scientific evidence on the clinical impact of this finding does not yet exist, PSMA-PET CT imaging is already widely used in the primary staging of prostate cancer in the Netherlands. For nodal staging, the gold standard is a pelvic lymph node dissection (8,9). However, surgery is not without risk and a pelvic lymph node dissection is not indicated when the risk of nodal disease is low. Therefore, additional clinical nomograms were developed based on prediction models in order to estimate the risk of lymph node involvement, such as the Briganti (24), Partin (25), and Memorial Sloan Kettering Cancer Center (MSKCC) (26) nomograms. Thresholds (of over 5%) for the probability of lymph node invasion are used to decide whether lymph node dissection is necessary for nodal staging or can be omitted (8,9). In the future, an increase in the accuracy of nodal disease staging with enhanced imaging modalities (mpMRI, PSMA-PET and nano-MRI), will hopefully lead to a reduced need of pelvic lymph node dissection and, thereby, lead to lower treatment-related morbidity and health costs (27).

**Evolution of Treatment of primary localized prostate cancer**

Depending on the risk classification, morbidity and life expectancy of a patient, the urologist will inform the patient on suitable treatment options and specific treatment-related toxicity.

In the Netherlands, the emphasis lies on shared decision making between the patient and the clinical physician. Stam et al. created a decision-making aid for the treatment of prostate cancer. In order to make a well-considered treatment decision as a patient, early referral to the radiation oncologist in the decision-making process for the treatment of prostate cancer is beneficial (28).

Expectant management strategies such as active surveillance or watchful waiting can be considered in patients with low-risk disease or in case of severe comorbidities. Active surveillance was introduced to prevent overtreatment and consists of regular follow-up by the urologist including digital rectal examination, PSA testing, mpMRI and prostate biopsies, with adaption to active treatment once clinical progression is observed. Active treatment is performed in patients with localized disease and consist of radical prostatectomy, brachytherapy, or external beam radiotherapy (EBRT) with or without pelvic lymph node dissection and with or without the administration of (neo)adjuvant hormonal therapy (8,9,17). In radical prostatectomy, the prostate and seminal vesicles are surgically removed by the urologist with an open, laparoscopic or, most commonly used, robot-assisted approach. Postoperative complications such as severe blood loss requiring blood transfusion, infection, or urinary leakage due to failure of the anastomosis are limited. Treatment-related toxicity is more common and mainly consists of urinary incontinence and erectile dysfunction. Nerve sparing techniques to prevent erectile dysfunction are carried out if desired by the patient and if technically possible, depending on the extension of local disease (8,9). Radiotherapy can be delivered internally as brachytherapy with permanent implantation of radioactive seeds (Low Dose Rate (LDR)) into the prostate, which is more invasive when compared to externally delivered radiotherapy (29). At current practise, EBRT requires more visits (5-20) to the radiotherapy department. The number of fractions is dependent on the disease stage and radiotherapy department. Radiotherapy-related toxicity consist of genitourinary toxicity with predominantly urinary frequency and urinary retention. Gastrointestinal toxicity including rectal bleeding and proctitis is overall less common. Erectile dysfunction is frequently observed, which is also strongly dependent on baseline erectile function, the use of (neo-)adjuvant hormonal therapy and patients age (8,9). Local tumor staging has become more accurate with the introduction of mpMRI. Knowledge on the localization, size and extend of the tumor (i.e., the presence of extraprostatic extension) is used to determine the possible treatment strategies, as well as the patient' preference. In case of extraprostatic extension, the urologist may decide not to perform a nerve sparing approach in radical prostatectomy or decide not to perform surgery at all (30). Over the years, treatment options for prostate cancer have advanced significantly and the life expectancy of men diagnosed with prostate cancer improved. Therefore, secondary endpoints such as treatment-related toxicity and patient reported quality of life are of increasing importance.

Randomized controlled trials comparing different treatment modalities for primary prostate cancer are difficult to conduct on a large scale. The ProtecT trial compared active surveillance with radical prostatectomy and EBRT in predominantly low- and intermediate-risk patients. Prostate cancer-specific mortality was comparable between all treatment arms (31). Initiatives that provide large scale data, such as the Utrecht Prostate Cohort for Cancer Treatment Intervention Studies and Long-term Evaluation Cancer (UPC), with a trials within cohorts design (TWICS), will enable researchers to compare newer radiotherapy schedules with radical prostatectomy and allow for comparison in higher risk groups of localized prostate cancer (32).

**External beam radiotherapy**

External beam radiotherapy, often combined with hormonal therapy, is one of the standard treatment options for intermediate- and high-risk localized prostate cancer. Depending on the disease stage, patient and physicians' preference, (neo-)adjuvant hormonal therapy is given for a duration between six and 36 months (17,33). Prior to CT-guided radiotherapy, gold fiducial markers are implanted in the prostate to set-up each treatment session and minimizing interfraction position uncertainty (34). Linear accelerators with Intensity Modulated Radiation Therapy (IMRT) (35) or Volumetric Modulated Arc Therapy (VMAT) techniques are used to deliver highly conformal radiation beams (36). Besides the enhancement of the diagnostic work-up, the introduction of mpMRI also improved radiation treatment strategies. Image guided radiotherapy (IGRT) is the state-of-the-art in radiotherapy for prostate cancer (37). Imaging (CT and MRI) is used to delineate the gross tumor volume (GTV), the clinical target volume (CTV), the planning target volume (PTV) and the organs at risk (OAR). Dose-constraints to the OAR are used to limit treatment-related toxicity. With mpMRI, the delineation of OAR improved and delineation of the intraprostatic lesions and urethra, albeit difficult, became possible (38). MRI guided radiotherapy (MRIgRT) was introduced with the development of a system combining a linear accelerator and MRI scanner, i.e., the MR-Linac (39) and MRIdian (40), which allow for precision radiotherapy with smaller margins and, therefore, higher doses per fraction and focal boosting are possible. Additionally, with MRIgRT the use of gold fiducial markers can be omitted. The MIRAGE trial compares MRIgRT with CT-guided radiotherapy and showed promising results in the reduction of acute treatment-related toxicity and improved quality of life with MRIgRT (41). Moreover, MRIgRT enables nerve sparing radiotherapy approaches in prostate cancer, which is being tested, for favorable risk patients in the phase II ERECT trial (42).

**Hypofractionation**

Stereotactic Body Radiation Therapy (SBRT) is a radiotherapy technique that delivers high doses with high precision. SBRT is used to administer (ultra-)hypofractionation schedules

for the treatment of localized prostate cancer (43). In radiotherapy, the Linear Quadratic Model is used to compare the effectivity of different fractionation schedules (44). Prostate cancer has a low α/β ratio and, therefore, benefits of larger fractionation sizes, which is one of the arguments for moderate and ultra-hypofractionation. These schedules are used to increase the biologically effective dose to the tumor, and, thereby, potentially improving oncological outcomes, without increasing toxicity (43,45). The surrounding organs (rectum and bladder) have a higher α/β ratio and are, therefore, less responsive to the larger fraction sizes compared to prostate cancer, which is another argument in favour of hypofractionation. Moreover, healthy tissue is believed to have a better repair mechanism compared to cancer cells and allows for recovery in between fractions (43). Moderate hypofractionation was tested in multiple phase III randomized controlled trials (HYPRO trial (46), CHHiP trial (47)) and showed non-inferiority when compared to conventional fractionation schedules. Ultra-hypofractionation (i.e., HYPO-RT-PC trial (48) and PACE B (49)) has shown to be non-inferior to conventional fractionation schedules, with comparable toxicity and with fewer patient visits at lower health cost (50). Ultra-hypofractionation (35-36.25 Gy in five fractions) for the treatment of low- and intermediate-risk prostate cancer was included in The American Society for Radiation Oncology (ASTRO), ASCO, and American Urological Association (AUA) Evidence-Based Guidelines in 2018 (51).

**Focal boosting (FLAME trial)**

Whole-gland dose escalation in EBRT for prostate cancer has proven to be effective, with a dose-response relation between an increased dose to the prostate and biochemical-disease free survival. However, further escalation of the dose to the entire prostate has shown to increase treatment-related toxicity, as the organs at risk are also subjected to a higher radiation dose (52). Local recurrences following EBRT are often located at the primary tumor site (53,54), this finding suggests that eradication of the primary tumor was insufficient. Cellini et al. (55) histopathologically confirmed that local recurrences predominantly originate at the primary tumor site. In light of this, the hypothesis arises whether increasing the dose to the dominant intraprostatic lesions could improve local tumor control and, thereby, potentially improve regional and distant metastatic failure rates, without deteriorating treatment-related toxicity and quality of life (56). With the introduction of mpMRI, the delineation of intraprostatic lesions became possible. Singh et al. showed that focal boosting up to 95Gy is feasible in terms of treatment planning, without severe toxicity in three patients (57). The concept of adding a focal boost to the intraprostatic tumor lesion has been tested with various radiotherapy techniques in pilot studies and showed promising results (58). The phase III randomized controlled ASCENDE-RT trial investigated the concept of boosting for prostate cancer using a whole-gland LDR brachytherapy boost and showed an increased biochemical disease-free survival of five

percent compared to the standard treatment arm (59). Another form of radiotherapy is High Dose Rate (HDR) brachytherapy, using a radioactive source to deliver brachytherapy into the prostate temporarily, this technique is mostly used in the recurrent setting of prostate cancer, however, in primary setting it can be used to deliver a focal boost to the dominant intraprostatic lesion, which is being tested in the TARGET trial (NCT01802242).

In 2009, the phase III randomized controlled Focal Lesion Ablative Microboost in prostatE cancer (FLAME) trial was introduced to test the concept of focal boosting in EBRT for intermediate- and high-risk localized prostate cancer patients by adding a focal boost up to 95 Gy to the intraprostatic lesion compared to conventionally fractionated EBRT of 77 Gy (35 fractions) to the entire prostate (56).

## AIM AND OUTLINE OF THE THESIS

**Objectives**

The general objective of this thesis was to investigate whether the concept of focal boosting in prostate cancer is beneficial in terms of oncological outcomes and, secondary, to determine if focal boosting can be applied without deteriorating treatment-related toxicity and quality of life. This thesis will contribute to, and has the potential to change, primary treatment for localized prostate cancer. Moreover, this thesis will change the scope of treatment in the radiotherapy field for primary prostate cancer and will help answer the question whether focal boosting in EBRT for localized prostate cancer will reduce local failure, and thereby prevent (distant) metastases that might, subsequently, lead to decreased prostate cancer-specific or overall survival.

**Specific aims**

The FLAME trial was designed to investigate the benefit in five-year biochemical disease-free survival of a focal boost up to 95 Gy compared to conventional fractionated EBRT of 77 Gy for intermediate-risk and predominantly high-risk localized prostate cancer (**chapter 2**). Secondary endpoints were treatment-related toxicity and patient reported quality of life (**chapter 2**). In order to investigate whether the addition of a focal boost to the conventional fractionation schedule would lead to additional toxicity, a dose-effect model for gastrointestinal (**chapter 3**) and genitourinary (**chapter 4**) toxicity was created. Secondary to biochemical disease-free survival, the patterns of failure following EBRT with or without a focal boost were investigated (**chapter 2 and 5**). The thesis will be concluded with a General Discussion (**chapter 6**).

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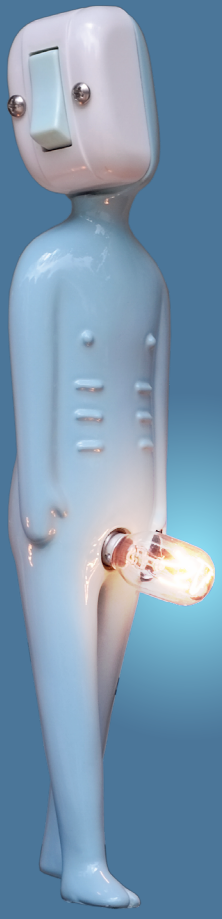

CHAPTER 2

# Focal boost to the intraprostatic tumor in external beam radiotherapy for patients with localized prostate cancer: results from the FLAME randomized phase III trial

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## ABSTRACT

**Purpose**

This study investigates whether focal boosting of the macroscopic visible tumor with external beam radiotherapy (EBRT) increases biochemical disease-free survival (bDFS) in patients with localized prostate cancer.

**Patients and methods**

In the phase 3, multicenter, randomized controlled FLAME trial, 571 patients with intermediate- and high-risk prostate cancer were enrolled between 2009 and 2015. Patients assigned to standard treatment received 77 Gy (fractions of 2.2 Gy) to the entire prostate. The focal boost arm received an additional simultaneous integrated focal boost up to 95 Gy (fractions up to 2.7 Gy) to the intraprostatic lesion visible on multiparametric MRI. Organ at risk constraints were prioritized over the focal boost dose. The primary endpoint was five-year bDFS. Secondary endpoints were disease-free survival (DFS), prostate cancer-specific survival (PCSS), overall survival (OS), toxicity and health-related quality of life (HRQoL).

**Results**

Median follow-up was 72 months. Biochemical DFS was significantly higher in the focal boost compared to the standard arm (HR 0.45, 95% CI 0.28-0.71, $p<0.001$). At five year follow-up bDFS was 92% and 85%, respectively. We did not observe differences in PCSS ($p=0.49$) and OS ($p=0.50$). The cumulative incidence of late genitourinary and gastrointestinal toxicity grade ≥2 was 23% and 12% in the standard arm versus 28% and 13% in the focal boost arm, respectively. Both for late toxicity as HRQoL, differences were small and not statistically significant.

**Conclusion**

The addition of a focal boost to the intraprostatic lesion improved bDFS for patients with localized intermediate- and high-risk prostate cancer without impacting toxicity and QoL. The FLAME study shows that a high focal boost strategy to improve tumor control and respecting organ at risk dose constraints, is effective and safe.

## CONTEXT

Is it possible to improve biochemical disease-free survival by adding a focal boost to the intraprostatic lesion to whole gland external beam radiotherapy for patients with intermediate- and high-risk prostate cancer?

A focal boost to the intraprostatic lesion improves biochemical disease free survival in patients with localized intermediate- and high-risk prostate cancer.

By prioritizing the dose constraints of the organs at risk over the focal boost dose that could be achieved, toxicity or quality of life did not deteriorate.

Addition of a focal boost may be considered for patients treated by external beam radiotherapy for localized intermediate- and high-risk prostate cancer.

## INTRODUCTION

A dose-response relationship has been described for external beam radiotherapy (EBRT) for localized prostate cancer. Whole-gland dose-escalation up to 80 Gy is considered effective and safe (1-4). Further dose increase to the entire prostate results in higher toxicity rates (2, 5-7). Local recurrences of prostate cancer following radiotherapy often originate from the primary tumor site (8). Therefore, focal boosting has been proposed to increase biochemical disease-free survival (bDFS) without increasing toxicity (9). The dose to the macroscopic visible tumor on multiparametric magnetic resonance imaging (mpMRI) is increased without increasing the dose to the organs at risk (OAR). A systematic review identified 13 single arm studies that assessed the efficacy and safety of a focal boost using EBRT, low-dose rate brachytherapy (LDR-BT) or high dose rate brachytherapy (HDR-BT). The pooled median five-year bDFS of the 13 studies was 85% (range 79% - 100%) (10).
To test the hypothesis that focal dose escalation improves bDFS in intermediate and high-risk prostate cancer, the Focal Lesion Ablative Microboost in Prostate Cancer (FLAME) trial was conducted, comparing EBRT of 77 Gy in 35 fractions with or without a simultaneous integrated focal boost up to 95 Gy (11). As the benefit of focal boosting was unproven, the trial was designed deliberately to avoid additional toxicity by the focal boost. Therefore, pre-specified dose constraints to organs at risk were strictly adhered to, reducing the focal boost dose if required.

## PATIENTS AND METHODS

**Study design**

The multicenter, phase 3, randomized controlled FLAME trial was carried out in the University Medical Center (UMC) Utrecht, the Netherlands Cancer Institute (NKI) in Amsterdam, the Radboudumc in Nijmegen in The Netherlands and the University Hospitals Leuven (UZL) in Belgium. The research protocol was approved by the medical ethics committee of the UMC Utrecht (NL26038.041.08) for The Netherlands and UZL for Belgium (B322201110225).

The FLAME study has been registered: https://clinicaltrials.gov/ct2/show/NCT01168479

**Participants**

Since 2009, patients with intermediate- and high-risk localized prostate cancer were included according to the Ash criteria (12). Since the Ash criteria are no longer in use in today's practice, we used the European Association of Urology (EAU) risk classification (13) for further analyses.

Exclusion criteria were: WHO performance score >2, IPSS score ≥20, evidence of lymph node involvement or distant metastases, a history of pelvic radiation, prostatectomy, trans urethral resection of the prostate (TURP) less than three months prior to radiotherapy and patients who were not able to undergo MR imaging. All included patients provided written informed consent.

**Randomization and masking**

The patients were randomized in a 1:1 ratio to the standard or focal boost arm. Randomization and stratification took place by an independent trial center at the UMC Utrecht, with a minimization procedure using center as minimization factor, ensuring balance within each stratum and overall balance. Contrary to what was intended in the trial protocol, hormonal therapy and TURP were not used as minimization factors. Nonetheless, post-hoc stratification for hormonal therapy and TURP showed well balanced groups (Supplementary – Table 1 & 2). The FLAME trial was blinded for patients, blinding for the investigator was not possible as the treating physicians were involved in the radiotherapy planning.

**Procedures**

Patients randomized to the standard treatment arm received conventionally fractionated EBRT consisting of 77 Gy in 35 fractions of 2.2 Gy (equivalent dose (EQD2) 81.8 Gy, assuming an α/β-ratio of 1.2) to the prostate. Patients assigned to the focal boost arm additionally received a simultaneous integrated focal boost up to 95 Gy to the macroscopic

tumor as visible on mpMRI, resulting in 35 fractions of up to 2.7 Gy (EQD2 115.8 Gy). The boost dose was reduced if required to meet the OAR constraints. The treatment planning, including dose constraints and achieved dose escalation has been described before (11, 14, 15) (Supplementary – Table 3). The mpMRI scans were performed in the four participating centers. Although the PI-RADS guidelines were published after the start of the FLAME trial, the mpMRI protocols were conform the PI-RADS recommendations (16, 17). Target volumes and the OAR were delineated on a planning CT and planning mpMRI scan. Intraprostatic lesions were contoured as GTV using T2-weighted, Diffusion Weighted Imaging and Dynamic Contrast Enhanced sequences. The GTV contouring has been analyzed before (18). There was no margin for clinical or planned target volume of the boost. The seminal vesicles were contoured according to clinical practice. Elective regional lymph node irradiation was not performed. Intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) were applied. Gold fiducial markers were implanted for position verification during treatment. (Neo)adjuvant hormonal therapy was prescribed according to clinical practice.

**Outcomes**

The primary endpoint was five-year bDFS, defined as time from randomization to biochemical recurrence. Biochemical recurrence was defined as the lowest prostate-specific antigen (PSA) value after treatment (PSA nadir) plus 2 ng/mL, according to the Phoenix criteria (19). Secondary outcomes were prostate cancer-specific survival (PCSS), overall survival (OS), toxicity and HRQoL. Disease-free survival (DFS) and distant metastases-free survival (DMFS), were described additionally, with failure defined as biochemical recurrence and/or evidence of recurrent disease on imaging or time to the first distant metastasis.

Genitourinary (GU) and gastrointestinal (GI) toxicity were assessed using the CTCAE version 3.0 (20). Toxicity was scored weekly during treatment, at one month, six months and yearly thereafter up to ten years.

To assess HRQoL, patients filled out the EORTC QLQ-PR25 (prostate specific) questionnaire at baseline, at one, six, 12, 24 and 60 months after treatment (21). Four domains; urinary symptoms, bowel symptoms, sexual activity and sexual functioning were addressed. Sexual activity and sexual functioning are presented for patients who did not receive hormonal therapy. HRQoL scores ranged from 0-100. For symptom scales (urinary and bowel) higher scores indicate more symptoms. For functioning scales (sexual activity and sexual functioning) higher scores indicate better functioning. A difference in scores of more than five points between treatment arms was considered clinically relevant.

**Statistical analyses**

The FLAME trial was designed to have 80% power to detect a 10% difference in five-year

bDFS between the treatment arms (alpha 0.05, one-sided). Assuming a five-year bDFS of 64% in the standard treatment arm (4), we calculated a sample size including 283 patients per arm. Primary analyses were performed according to intention-to-treat. We additionally performed a per protocol analysis.

We performed Kaplan-Meier analyses up to seven years with log-rank tests to assess differences in bDFS, DFS, PCSS and OS between treatment arms. Patients were censored at date of death or last follow-up. (Un)adjusted Cox regression models were performed for bDFS, DFS and DMFS, with adjustment for center, iPSA, T-stage, Gleason, age and duration of hormonal treatment (months). A competing risk analysis according to the Fine and Grey method was performed, with death by any cause as a competing risk (24).
We created a dose-response curve with the predicted probability of biochemical and distant metastatic failure up to seven years as a function of the near minimum (D98%) dose to the intraprostatic lesion using logistic regression.

Late toxicity was defined as toxicity from three months to five years after start of treatment. The differences in the cumulative incidence of late grade ≥2 and late grade ≥3 toxicity between treatment arms were calculated.
The observed mean HRQoL per domain over time were graphically presented. Additionally, we performed linear mixed effect models for repeated measurements to assess the impact of the focal boost on HRQoL up to five years after treatment, with fixed effects including randomization and time as interaction, duration of hormonal therapy, age and baseline HRQoL and patient ID as random effect.

Statistical analyses were performed with IBM SPSS Statistics 25, RStudio and SAS enterprise version 9.4.

## RESULTS

Between November 2009 and February 2015, 571 intermediate- and high-risk localized prostate cancer patients were randomized to the standard treatment (n=287) or focal boost arm (n=284). All patients had a potential follow-up of five years and median follow-up was 72 months (interquartile range 58-86). Patient and treatment characteristics were well balanced at baseline (Table 1). Hormonal treatment was given in 65% in both study arms, equally distributed. The mean age was 70 years (SD 6). Six patients with low-risk disease were excluded from the analyses as they did not fulfill the inclusion criteria (n=4 in standard treatment and n=2 in the focal boost arm). Twenty-nine patients (standard treatment arm

n=10 and focal boost arm n=19) were excluded from the per protocol analyses because they did not receive their assigned treatment (Figure 1). Eight patients (standard treatment (n=7), focal boost (n=1)) were excluded from the Kaplan-Meier and Cox regression analysis because they were not followed up actively.



**Table 1.** Patient and treatment characteristics by randomization arm

| Baseline | Standard treatment | Focal boost treatment |
|---|---|---|
| Number of Subjects (n) | 287 | 284 |
| Mean age in years (SD) | 70 (7) | 70 (6) |
| **Risk stratification (EAU criteria)** | N (%) | N (%) |
| Low-risk | 4 (1) | 2 (1) |
| Intermediate-risk | 43 (15) | 43 (15) |
| High-risk | 240 (84) | 239 (84) |
| **Centre** | N (%) | N (%) |
| UMC Utrecht | 160 (56) | 160 (56) |
| Netherlands Cancer Institute | 55 (19) | 54 (19) |
| University Hospitals Leuven | 47 (16) | 46 (16) |
| Radboudumc | 25 (9) | 24 (9) |
| **iPSA (ng/mL)** | | |
| Mean (SD) | 15.2 (14.9) | 16.3 (13.9) |
| **Clinical T-stage** | N (%) | N (%) |
| 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) |
| **Biopsy Gleason score** | N (%) | N (%) |
| < 7 | 55 (19) | 47 (17) |
| 7 | 139 (48) | 139 (49) |
| ≥ 8 | 93 (32) | 98 (35) |
| **N-stage** | N (%) | N (%) |
| cN0 | 226 (79) | 231 (81) |
| pN0 < 10 lymph nodes removed | 48 (17) | 33 (12) |
| pN0 ≥ 10 lymph nodes removed | 13 (5) | 20 (7) |
| **Hormonal therapy prescribed** | N (%) | N (%) |
| 18-36 months | 84 (29) | 96 (34) |
| 6-18 months | 32 (11) | 33 (12) |
| 6 months | 58 (20) | 50 (18) |
| No | 99 (35) | 98 (35) |
| Missing | 14 (5) | 7 (3) |
| **TURP*** | N (%) | N (%) |

**Table 1.** Continued

| Baseline | Standard treatment | Focal boost treatment |
|---|---|---|
| Yes | 41 (14) | 36 (13) |
| No | 246 (86) | 248 (87) |
| **Cardiovascular disease** | N (%) | N (%) |
| Yes | 155 (54) | 147 (52) |
| No | 132 (46) | 137 (48) |
| **Diabetes Mellitus** | N (%) | N (%) |
| Yes | 31 (11) | 30 (11) |
| No | 256 (89) | 254 (89) |

* TURP = trans urethral resection of the prostate

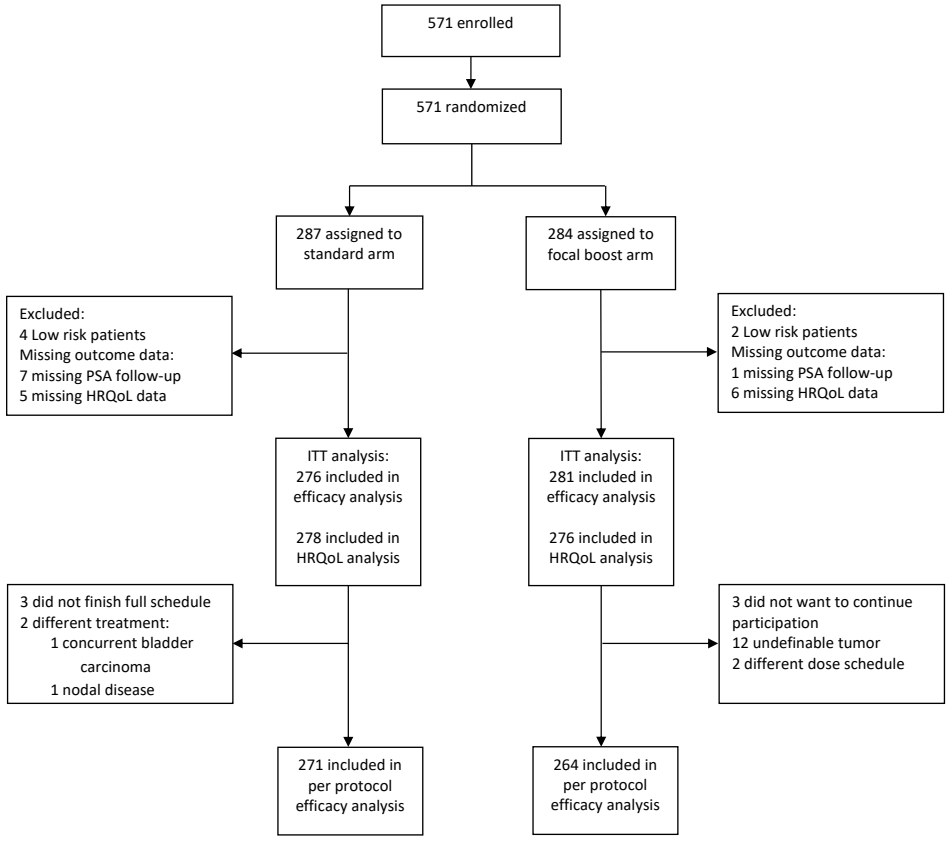


**Figure 1.** Trial profile

We observed a five-year bDFS of 85% (38 events; 95% CI 80%-89%) in the standard arm and 92% (21 events; 95% CI 87-94%) in the focal boost arm, significantly different between groups, (difference: 7% 95% CI 4.2-9.8). The Kaplan Meier curves showed significantly improved bDFS (log-rank p<0.001) and DFS (log-rank p<0.001) in the focal boost arm up to seven years. DMFS showed no difference (log-rank p=0.26) (Figure 2). We did not find differences in OS (log-rank p=0.50) and PCSS (log-rank p=0.49) (Supplementary – Figure 1). Adjusted Cox regression analysis showed that biochemical failures were reduced by half (hazard ratio (HR) 0.45 (95% CI 0.29-0.71, p<0.001), when comparing the focal boost to standard treatment (Table 2). These analyses showed comparable results for DFS (HR 0.48 (95 CI 0.32-0.74, p<0.001), while DMFS showed no statistically significant difference (HR 0.72 (95 CI 0.43-1.22, p=0.23). Adjusted Cox regression analysis showed a HR of 1.26 (95% CI 0.83-1.92, p=0.27) for OS and 0.69 (95% CI 0.27-1.79, p=0.45) for PCSS. Results of the per protocol analysis did not differ from the intention-to-treat analysis (Supplementary – Figure 2 & 3, Table 4). Also, a competing risk analysis showed similar results (Supplementary – Table 4).

The biochemical failure rate up to 7 years is presented as a function of achieved dose to the GTV in Figure 3. The distant metastases failure rate as a function of GTV dose is shown in the Supplementary – Figure 4. Late GU and GI toxicity grade ≥2 and grade ≥3 differences were small and not statistically significant different. Cumulative incidences per treatment arm are presented in Table 3. One patient in the focal boost arm developed grade 4 GU toxicity, three years after treatment. He suffered from severe urinary incontinence for which he underwent a permanent urinary diversion. No grade 4 GI toxicity occurred.

We did not observe statistically significant differences in HRQoL domains between both treatment arms (Supplementary – Table 5). The mean (95% CI) HRQoL per domain per time point is shown in Supplementary – Figure 5. The response rate was at least 85% in the first year and decreased to 55% at five years. Urinary HRQoL deteriorated one month after treatment and improved within one year in both treatment arms. Bowel HRQoL deteriorated less than five points from baseline in both arms and remained at a similar level during follow-up. Sexual activity in patients without hormonal therapy never deteriorated >5 points from baseline for both arms.

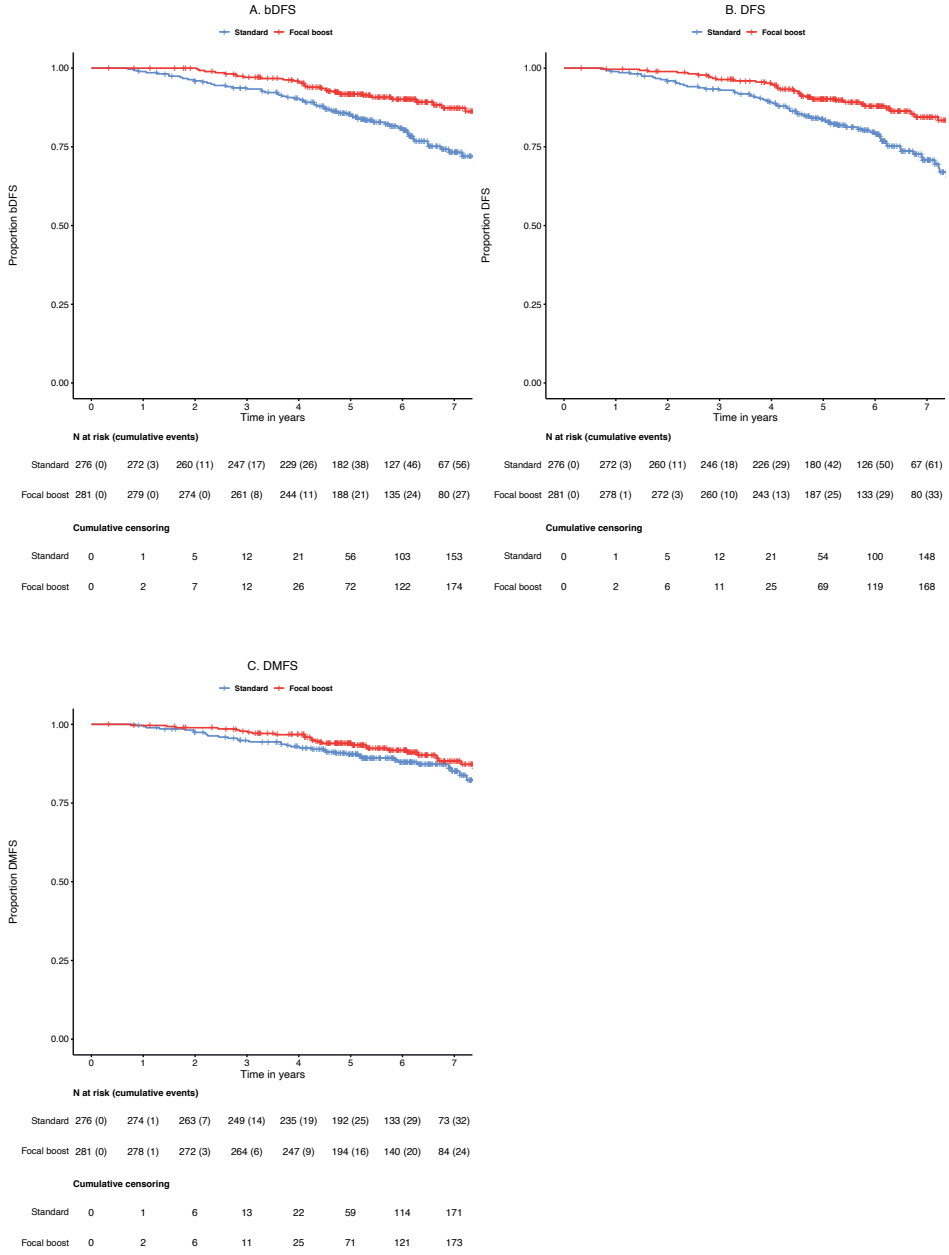


**Figure 2.** Kaplan-Meier curves up to seven years for A. biochemical disease-free survival (bDFS) (p<0.001), B. disease-free survival (DFS) (p<0.001) and C. distant metastases-free survival (DMFS) (p=0.26) comparing the standard treatment of 77 Gy in 35 fractions to the whole prostate with an additional focal boost to the macroscopic visible tumor up to 95 Gy

**Table 2.** Results of Cox regression analysis for biochemical disease-free survival (bDFS), disease-free survival (DFS) and distant metastases-free survival (DMFS) unadjusted and adjusted for centre, age, hormonal treatment, T-stage, initial PSA and Gleason score

| | bDFS | | | DFS | | | DMFS | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR* | 95% CI | p-value | HR* | 95% CI | p-value | HR* | 95% CI | p-value |
| Unadjusted | 0.46 | 0.30 – 0.72 | <0.001 | 0.50 | 0.33 – 0.75 | <0.001 | 0.75 | 0.45-1.24 | 0.26 |
| Adjusted | 0.45 | 0.28 – 0.71 | <0.001 | 0.48 | 0.32 – 0.74 | <0.001 | 0.72 | 0.43-1.22 | 0.23 |

* Hazard ratio

**Table 3.** Difference in cumulative incidence of late* grade ≥ 2 and grade ≥ 3 genitourinary and gastrointestinal toxicity

| | Genitourinary toxicity | | | | Gastrointestinal toxicity | | | |
|---|---|---|---|---|---|---|---|---|
| | 77Gy | 95Gy | Difference in % (95% CI) | p-value | 77Gy | 95Gy | Difference in % (95% CI) | p-value |
| Grade ≥ 2 | 23.0 | 27.8 | 4.8 (-2.3 – 12.0) | 0.19 | 12.2 | 12.7 | 0.5 (-5.0 – 5.9) | 0.86 |
| Grade ≥ 3 | 3.5 | 5.6 | 2.1 (-1.3 – 5.6) | 0.22 | 1.4 | 1.4 | 0 (-1.9 – 2.0) | 0.99 |

*Late toxicity defined as toxicity from three months to five years after start of treatment

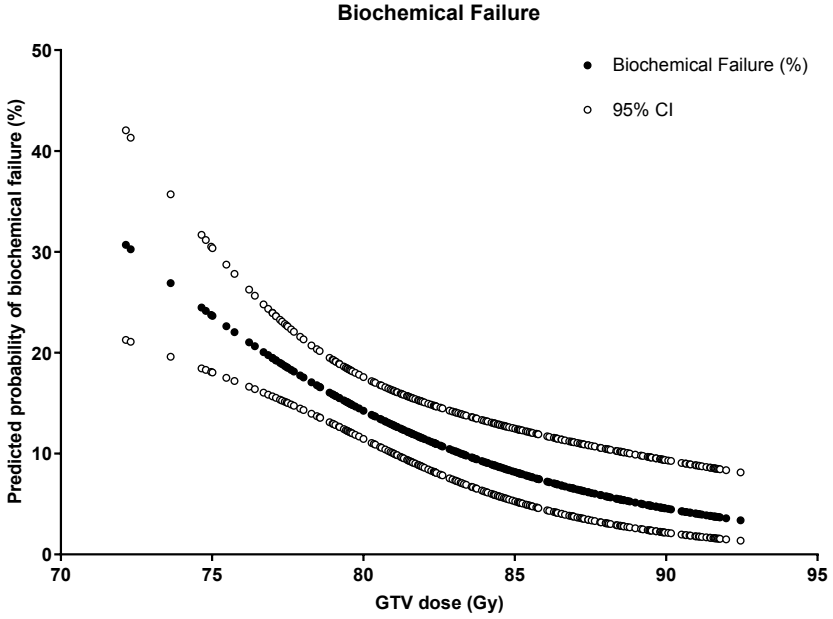


**Figure 3** – Predicted probability of biochemical failure up to 7 years as a function of achieved dose to the GTV (D98%; Gy)

## DISCUSSION

The FLAME trial is the first phase 3 RCT to show that the addition of a focal boost to the intraprostatic lesion(s) in EBRT for prostate cancer significantly improves five-year bDFS, from 85% in the standard arm to 92% in the focal boost arm. Differences in toxicity were small and not statistically significant. For late GU (urethra-related) toxicity a median follow-up time of 6 years is relatively short and longer follow-up is required. In the FLAME trial a urethra dose constraint was not used. However, such a constraint was incorporated in our subsequent focal boost studies. The comparable toxicity was achieved by strictly respecting dose constraints to OARs, reducing the focal boost dose if necessary. The 7% increase in bDFS therefore likely underestimates the positive effect of focal boosting to 95 Gy. Indeed, a clear decrease of biochemical failure rate with increasing boost dose was found. There was no significant difference in PCSS and OS. The follow-up time was relatively short to draw conclusions on survival for prostate cancer and the study was not powered for these endpoints. Although there was no significant difference in DMFS, the data suggest a dose response relation for distant metastatic failure. However, a longer follow-up is required to confirm this.

Compared to previous trials, the FLAME trial was heavily weighted to high-risk patients (84%). Nevertheless, bDFS in the standard treatment arm was high compared to four whole-gland dose-escalation RCTs including low-, intermediate- and high-risk patients, with five-year bDFS rates ranging from 64-76.5% in the dose-escalation arms (2, 4, 6). In the MD Anderson trial, a six-year freedom from failure of 70% was observed in the dose-escalation arm (1). The high overall bDFS in the FLAME trial is likely explained by improved disease staging prior to treatment. Also, the mild hypofractionation (2.2 Gy per fraction) in both arms, resulted in a higher EQD2 of 81.8 Gy to the whole prostate, compared to whole-gland dose escalation trials (1-4). In the FLAME trial biochemical recurrence started after one year, suggesting that high-risk prostate cancer is not necessarily metastasized at time of diagnosis. The addition of (neo)adjuvant hormonal therapy may play a role in delaying biochemical failure, although 35% of the patients in both arms did not receive hormonal therapy.

A brachytherapy boost is another strategy to increase the dose. The ASCENDE-RT trial showed that a whole-gland LDR brachytherapy boost combined with hormonal therapy, leads to an improved bDFS compared to whole-gland EBRT. However, this came at the cost of increased five-year grade 3 GU toxicity (25, 26). Our results suggest that the same positive effect can be achieved without additional toxicity by limiting the boost to the intraprostatic lesion(s). In the FLAME trial, standard modern day treatment planning techniques such as

IMRT and VMAT on conventional linear accelerators (with on-board imaging) were used. Now that the concept of focal boosting has been demonstrated to benefit bDFS, improved EBRT planning techniques (14) or the use of a focal boost with brachytherapy, such as investigated in the TARGET trial (NCT01802242) (27), can be effective in depositing the high boost dose without exceeding OAR constraints.

In 2009 when the FLAME trial started, a 35-39 fractions schedule was standard. Large randomized Phase III hypofractionation trials, such as the CHiPP and HYPRO trials (28, 29) showed that hypofractionated EBRT in 2.4-3.4 Gy fractions is equivalent to conventionally fractionated (1.8-2 Gy) EBRT. Around 2018 the schedule of 20 times 3Gy in 4-5 weeks (EQD2 78.8 Gy) became the new standard (30). The results of the FLAME trial also indicate that the current standard, moderately hypofractionated 20 times 3 Gy, could be improved by (focal) dose escalation.

A meta-analysis of randomized trials looking at dose response and fractionation sensitivity of prostate EBRT indicated a shallow, but highly significant, dose response relationship (31) . Although Vogelius et al. suggested saturation might be present in the dose effect at an EQD2 of >80 Gy, the FLAME trial (EQD2Gy 115.8 Gy a/b ratio 1.2 Gy) and ASCENDE RT trial (50 Gy + 115 Gy brachytherapy boost) proved otherwise. Dose escalation will result in better outcome, however high doses are needed.

For low and intermediate prostate cancer the HYPO-RT-PC trial showed that extreme hypofractionation is non-inferior to conventional fractionated radiotherapy in terms of failure free survival and late toxicity. Acute toxicity was equal in PACE-B, however the HYPO-RT-PC showed more pronounced acute toxicity (32, 33). In 2018, the ASTRO, ASCO, and AUA Evidence-Based Guideline stated that, extreme hypofractionated 35 -36,25 Gy in 5 fractions may be offered to low- and intermediate-risk prostate cancer patients (30). However, this does not apply for high-risk and most likely a higher dose is needed. Several studies use focal dose escalation with a boost of 38-50 Gy. (NCT01409473, NCT01856855, NCT02145494, NCT01976962, NCT04245670, ISRCTN04483921, NCT02254746, NCT04045717, NCT02853110). The prospective phase II Hypo-FLAME trial investigated the safety of the technique of the FLAME trial with extreme hypofractionation (34). Mostly high-risk (75%) patients were treated with 35 Gy in 5 weekly fractions to the whole prostate gland with an integrated boost up to 50 Gy to the mpMRI-defined tumor(s). The technique proved safe without severe acute GI or GU toxicity.

A limitation of the FLAME study was missing toxicity data, as described previously (15). We do not expect this to have influenced the cumulative incidences of late toxicity. This is

supported by an equal number of missing data in both arms. Secondly, the PIRADS recommendations were published after the start of the FLAME trial and gross tumor volume (GTV) contouring guidelines are not available for prostate cancer, resulting in interobserver variability (35). Nonetheless, we did find a significant increase in bDFS in the focal boost arm.
Due to the pragmatic and practice-based approach of the trial, each center used their own OAR constraints. In addition all centers added a high dose constraint for the rectum and bladder (D1cc rectum max 77Gy and D1cc bladder max 80Gy). As the study arms were stratified for center at randomization, center-specific constraints are not likely to have influenced the comparison of the two study arms.

An inherent limitation due to the long duration of follow-up is the change in practice over time. The FLAME trial started in 2009 and we used a pragmatic approach according to clinical practice at the time. (Neo)adjuvant hormonal therapy was given according to clinical practice. We did not collect the percent positive biopsies and were therefore not able to calculate the UCSF-CAPRA score (36). The International Society of Urologic Pathology (ISUP) (37) score was implemented after patient inclusion in the FLAME trial, in the FLAME trial only the Gleason sum score was registered. Patients were staged according to clinical practice, imaging with or without a subsequent lymph node dissection. Most patients were included before a PSMA-PET scan was available. However, these limitations were similar in both treatment arms and we do not believe it influenced our findings.
Strengths of our study are the large number of patients, the multicenter collaboration and the high treatment compliance. PSA follow-up to assess the presence of bDFS was carried out thoroughly with minimal missing data, and the response rates of the HRQoL questionnaires were satisfying. Additionally, standard modern day radiotherapy techniques were used and no additional technology or equipment was required. Thus, implementation of a focal boost strategy does not lead to additional costs.
Although there was no survival benefit observed up till now, the reduction of biochemical recurrence by 50%, would probably benefit patients and their QoL. Biochemical recurrence means intensified follow-up and diagnostic exams with associated anxiety and eventually additional treatments with subsequent toxicity. Especially when this reduction in recurrence can be achieved without impacting toxicity or HRQoL compared to standard treatment and at no additional costs.

In conclusion, the FLAME trial showed that a focal boost to a high dose improves bDFS in intermediate- and high-risk localized prostate cancer, without additional toxicity. Focal dose escalation in (extreme) hypofractionated schedules should be further explored. As we observed a clear dose-response relation, further improvement of tumor control may be feasible when more advanced techniques allow a higher boost dose.

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# SUPPLEMENTARY MATERIAL

**Table S1.** Stratification of patient and treatment characteristics by hormonal treatment

| Baseline | | No hormonal treatment | | | | Hormonal treatment | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Standard treatment | | Focal boost treatment | | Standard treatment | | Focal boost treatment | |
| **Age in years, mean (SD)** | | 71 | 6 | 71 | 5 | 70 | 7 | 70 | 6 |
| EAU n (%) | Low-risk | 3 | 3.1% | 1 | 1.1% | 1 | 0.5% | 0 | 0% |
| | Intermediate-risk | 30 | 31.3% | 30 | 31.9% | 11 | 5.8% | 14 | 7.5% |
| | High-risk | 63 | 65.6% | 63 | 67.0% | 177 | 93.7% | 173 | 92.5% |
| Centre n (%) | UMC Utrecht | 74 | 77.1% | 74 | 78.7% | 84 | 44.4% | 84 | 44.9% |
| | Netherlands Cancer Institute | 6 | 6.3% | 7 | 7.4% | 41 | 21.7% | 38 | 20.3% |
| | University Hospitals Leuven | 5 | 5.2% | 3 | 3.2% | 50 | 26.5% | 51 | 27.3% |
| | Radboudumc | 11 | 11.5% | 10 | 10.6% | 14 | 7.4% | 14 | 7.5% |
| **iPSA (ng/mL) mean (SD)** | | 12.4 | 8.7 | 13.2 | 10.8 | 16.6 | 17.1 | 18.1 | 15.0 |
| Clinical T-stage n (%) | T1c | 18 | 18.8% | 17 | 18.3% | 7 | 3.7% | 4 | 2.1% |
| | T2a | 17 | 17.7% | 16 | 17.2% | 13 | 6.9% | 12 | 6.4% |
| | T2b | 10 | 10.4% | 9 | 9.7% | 7 | 3.7% | 11 | 5.9% |
| | T2c | 16 | 16.7% | 16 | 17.2% | 18 | 9.6% | 25 | 13.4% |
| | T3a | 29 | 30.2% | 25 | 26.9% | 95 | 50.5% | 84 | 44.9% |
| | T3b | 6 | 6.3% | 10 | 10.8% | 39 | 20.7% | 47 | 25.1% |
| | T4 | 0 | 0% | 0 | 0% | 9 | 4.8% | 4 | 2.1% |
| N-stage n (%) | N0 | 89 | 92.7% | 87 | 92.6% | 134 | 71.3% | 141 | 75.4% |
| | pN0 < 10 lymph nodes removed | 5 | 5.2% | 3 | 3.2% | 43 | 22.9% | 30 | 16.0% |
| | pN0 ≥ 10 lymph nodes removed | 2 | 2.1% | 4 | 4.3% | 11 | 5.9% | 16 | 8.6% |
| Biopsy Gleason score n (%) | <7 | 33 | 34.4% | 31 | 33.0% | 22 | 11.6% | 16 | 8.6% |
| | 7 | 53 | 55.2% | 53 | 56.4% | 83 | 43.9% | 83 | 44.4% |
| | ≥ 8 | 10 | 10.4% | 10 | 10.6% | 84 | 44.4% | 88 | 47.1% |
| Diabetes Mellitus n (%) | No | 78 | 81.3% | 83 | 88.3% | 175 | 92.6% | 164 | 88.6% |
| | Yes | 18 | 18.8% | 11 | 11.7% | 14 | 7.4% | 21 | 11.4% |
| Cardiovascular disease n (%) | No | 33 | 34.4% | 37 | 39.4% | 92 | 48.9% | 92 | 49.7% |
| | Yes | 63 | 65.6% | 57 | 60.6% | 96 | 51.1% | 93 | 50.3% |
| TURP n (%) | No | 75 | 78.1% | 83 | 88.3% | 169 | 89.4% | 163 | 87.2% |
| | Yes | 21 | 21.9% | 11 | 11.7% | 20 | 10.6% | 24 | 12.8% |

* TURP = trans urethral resection of the prostate

**Table S2.** Stratification of patient and treatment characteristics by trans urethral resection of the prostate (TURP)

| Baseline | | No TURP | | | | TURP | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Standard treatment | | Focal boost treatment | | Standard treatment | | Focal boost treatment | |
| Age in years, mean (SD) | | 70 | 7 | 70 | 6 | 73 | 6 | 72 | 5 |
| EAU n (%) | Low-risk | 3 | 1.2% | 1 | 0.4% | 1 | 2.4% | 0 | 0% |
| | Intermediate-risk | 32 | 13.1% | 36 | 14.5% | 10 | 23.8% | 8 | 22.2% |
| | High-risk | 210 | 85.7% | 211 | 85.1% | 31 | 73.8% | 28 | 77.8% |
| Centre n (%) | UMC Utrecht | 128 | 52.2% | 131 | 52.8% | 32 | 76.2% | 29 | 80.6% |
| | Netherlands Cancer Institute | 43 | 17.6% | 42 | 16.9% | 4 | 9.5% | 4 | 11.1% |
| | University Hospitals Leuven | 50 | 20.4% | 52 | 21.0% | 5 | 11.9% | 2 | 5.6% |
| | Radboudumc | 24 | 9.8% | 23 | 9.3% | 1 | 2.4% | 1 | 2.8% |
| iPSA (ng/mL) | | 15.4 | 15.6 | 16.3 | 13.6 | 14.3 | 9.5 | 17.2 | 15.8 |
| Clinical T-stage n (%) | T1c | 17 | 7.0% | 16 | 6.5% | 8 | 19.0% | 5 | 14.3% |
| | T2a | 25 | 10.2% | 25 | 10.1% | 5 | 11.9% | 3 | 8.6% |
| | T2b | 13 | 5.3% | 18 | 7.3% | 5 | 11.9% | 2 | 5.7% |
| | T2c | 28 | 11.5% | 34 | 13.7% | 6 | 14.3% | 7 | 20.0% |
| | T3a | 111 | 45.5% | 100 | 40.3% | 14 | 33.3% | 12 | 34.3% |
| | T3b | 42 | 17.2% | 51 | 20.6% | 3 | 7.1% | 6 | 17.1% |
| | T4 | 8 | 3.3% | 4 | 1.6% | 1 | 2.4% | 0 | 0% |
| N-stage n (%) | N0 | 188 | 77.0% | 201 | 81.0% | 37 | 88.1% | 30 | 83.3% |
| | pN0 < 10 lymph nodes removed | 43 | 17.6% | 28 | 11.3% | 5 | 11.9% | 5 | 13.9% |
| | pN0 ≥ 10 lymph nodes removed | 13 | 5.3% | 19 | 7.7% | 0 | 0% | 1 | 2.8% |
| Biopsy Gleason score n (%) | <7 | 47 | 19.2% | 44 | 17.7% | 8 | 19.0% | 4 | 11.1% |
| | 7 | 118 | 48.2% | 120 | 48.4% | 20 | 47.6% | 18 | 50.0% |
| | ≥ 8 | 80 | 32.7% | 84 | 33.9% | 14 | 33.3% | 14 | 38.9% |
| Diabetes Mellitus n (%) | No | 219 | 89.4% | 218 | 88.3% | 36 | 85.7% | 31 | 88.6% |
| | Yes | 26 | 10.6% | 29 | 11.7% | 6 | 14.3% | 4 | 11.4% |
| Cardiovascular disease n (%) | No | 107 | 43.9% | 117 | 47.4% | 18 | 42.9% | 13 | 37.1% |
| | Yes | 137 | 56.1% | 130 | 52.6% | 24 | 57.1% | 22 | 62.9% |
| Hormonal treatment n (%) | No | 75 | 30.7% | 83 | 33.7% | 21 | 51.2% | 11 | 31.4% |
| | Yes | 169 | 69.3% | 163 | 66.3% | 20 | 48.8% | 24 | 68.6% |

**Table S3** - Dose constraints to organs at risk

| Structure name | Institute | Constraints |
|---|---|---|
| Rectum | All<br>UMCU | V77Gy<1cc<br>V50Gy < 50%; V72Gy < 5 % |
| | Leuven | V42.9Gy < 50%; V66.7Gy < 25% |
| | Netherlands Cancer Institute | Constraints on rectal wall |
| Rectal wall | All<br>Netherlands Cancer Institute | V77Gy<1cc<br>V64Gy < 35%; PRV 2 mm: V80Gy<1cc |
| | Radboudumc | PRV 2 mm: Dmean <30 Gy, V50Gy < 50%, V65Gy < 40%; V70Gy < 30%; V75Gy < 10% |
| Bladder | All<br>UMCU | V80Gy<1cc<br>< 10 % > 72 Gy |
| | Leuven | V66.7Gy < 50%; V71.4Gy < 25% |
| | Netherlands Cancer Institute | No additional constraints |
| | Radboudumc | V72Gy < 10% |
| Anal sphincter | Leuven | V38.1Gy 40%, D1cc < 77Gy |
| | Netherlands Cancer Institute | Dmean < 45Gy, Dmax < 60Gy' |
| Penile bulb | Leuven | Dmax 50Gy |
| Femoral heads | Leuven | Dmean < 28.6Gy; V47.6Gy < 10% |
| | Netherlands Cancer Institute | Dmax < 50Gy |
| | Radboudumc | V50Gy < 5% |

**Table S4.** Results of Cox regression analysis for bDFS, DFS and DMFS, crude and adjusted for centre, age, duration of hormonal treatment, timing of hormonal treatment (neo-adjuvant versus adjuvant), T stage, initial PSA and Gleason score

| | **Per protocol analysis** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **bDFS** | | | **DFS** | | | **DMFS** | | |
| | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** | **HR*** | **95% CI** | **p-value** |
| Crude | 0.45 | 0.28-0.71 | <0.001 | 0.50 | 0.32-0.76 | <0.001 | 0.74 | 0.44-1.24 | 0.25 |
| Fully Adjusted | 0.44 | 0.27- 0.70 | <0.001 | 0.48 | 0.31-0.75 | <0.001 | 0.72 | 0.43-1.23 | 0.23 |
| | **Competing risk analysis (based on ITT)** | | | | | | | | |
| | **bDFS** | | | **DFS** | | | **DMFS** | | |
| | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** | **HR*** | **95% CI** | **p-value** |
| Crude | 0.45 | 0.29- 0.70 | <0.001 | 0.49 | 0.32- 0.73 | <0.001 | 0.74 | 0.45-1.22 | 0.24 |
| Fully Adjusted | 0.43 | 0.27- 0.67 | <0.001 | 0.46 | 0.30- 0.71 | <0.001 | 0.69 | 0.41-1.16 | 0.16 |

**Table S5.** Mean differences in health-related quality of life (HRQoL) per domain per time point between treatment arms. Results of the linear mixed models for repeated measurements, adjusted for age, baseline HRQoL and hormonal treatment. Scores for HRQoL range from 0-100. Higher scores indicate more symptoms for urinary and bowel domains. For sexual activity and sexual functioning lower scores indicate worse symptoms. A difference in score of >5 between both treatment arms was considered clinically relevant.

| Follow-up (months) | | 1 | | 6 | | 12 | | 24 | | 60 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean | MD (95% CI) | Mean | MD (95% CI) | Mean | MD (95% CI) | Mean | MD (95% CI) | Mean | MD (95% CI) |
| Urinary | 77Gy | 29.4 | Ref | 20.5 | Ref | 19.3 | Ref | 19.1 | Ref | 20.3 | Ref |
| | 95Gy | 27.5 | -1.9 (-5.8 2.1) | 19.3 | -1.3 (-4.4 1.8) | 21.7 | 2.4 (-1.3 6.0) | 20.6 | 1.5 (-2.1 5.0) | 21.2 | 1.0 (-3.1 5.0) |
| Bowel | 77Gy | 8.6 | Ref | 7.5 | Ref | 7.5 | Ref | 8.8 | Ref | 8.3 | Ref |
| | 95Gy | 7.6 | -1.0 (-3.4 1.4) | 7.1 | -0.4 (-2.6 1.7) | 8.1 | 0.6 (-2.1 3.3) | 8.6 | -0.2 (-2.9 2.5) | 7.3 | -1.0 (-4.2 2.3) |
| SEAC* | 77Gy | 28.8 | Ref | 28.7 | Ref | 31.7 | Ref | 27.1 | Ref | 30.7 | Ref |
| | 95Gy | 31.0 | 2.2 (-2.7 7.1) | 29.5 | 0.8 (-4.9 6.6) | 27.7 | -4.0 (-9.8 1.9) | 27.9 | 0.8 (-4.9 6.5) | 27.5 | -3.2 (-10.1 3.7) |
| SEFU* | 77Gy | 66.7 | Ref | 61.3 | Ref | 62.4 | Ref | 53.0 | Ref | 52.5 | Ref |
| | 95Gy | 67.5 | 0.8 (-6.2 7.7) | 61.3 | 0 (-8.8 8.7) | 57.8 | -4.6 (-13.7 4.4) | 59.8 | 6.8 (-2.6 16.2) | 53.4 | 0.9 (-13.0 14.7) |

MD = mean difference, Ref = reference category (standard arm), 77 Gy = standard arm, 95 Gy = focal boost arm, SEAC = sexual activity, SEFU = sexual functioning
For HRQoL analysis, 11 patients (n=5 standard treatment, n=6 focal boost) were excluded since no HRQoL data was available
* Sexual activity and sexual functioning are presented exclusively for patients who did not receive hormonal therapy

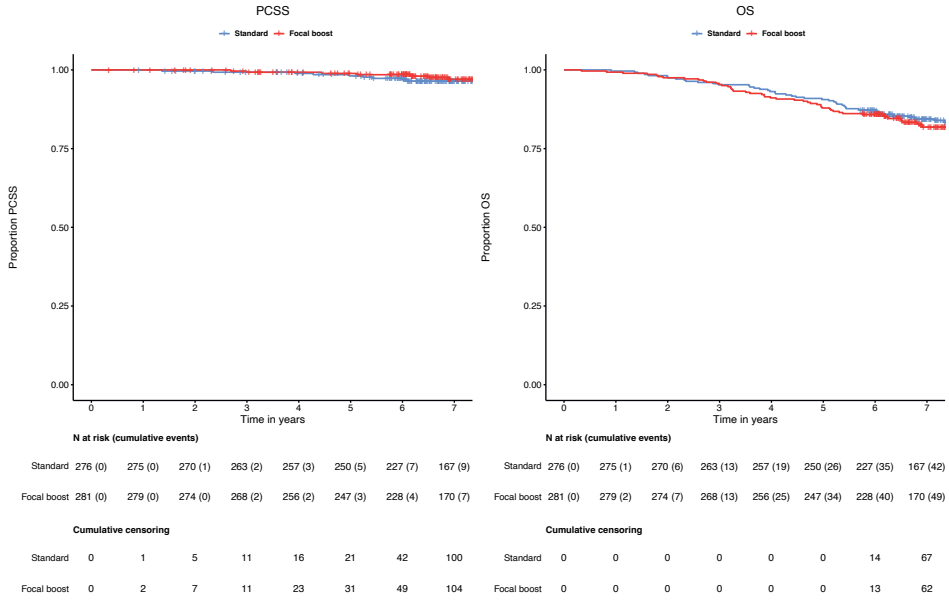



**Figure S1.** Kaplan-Meier curves for prostate cancer-specific survival (PCSS) (p=0.49) and overall survival (OS) (p=0.50) comparing the standard treatment of 77 Gy in 35 fractions to the whole prostate with an additional focal boost to the macroscopic visible tumor up to 95 Gy based on ITT analysis.

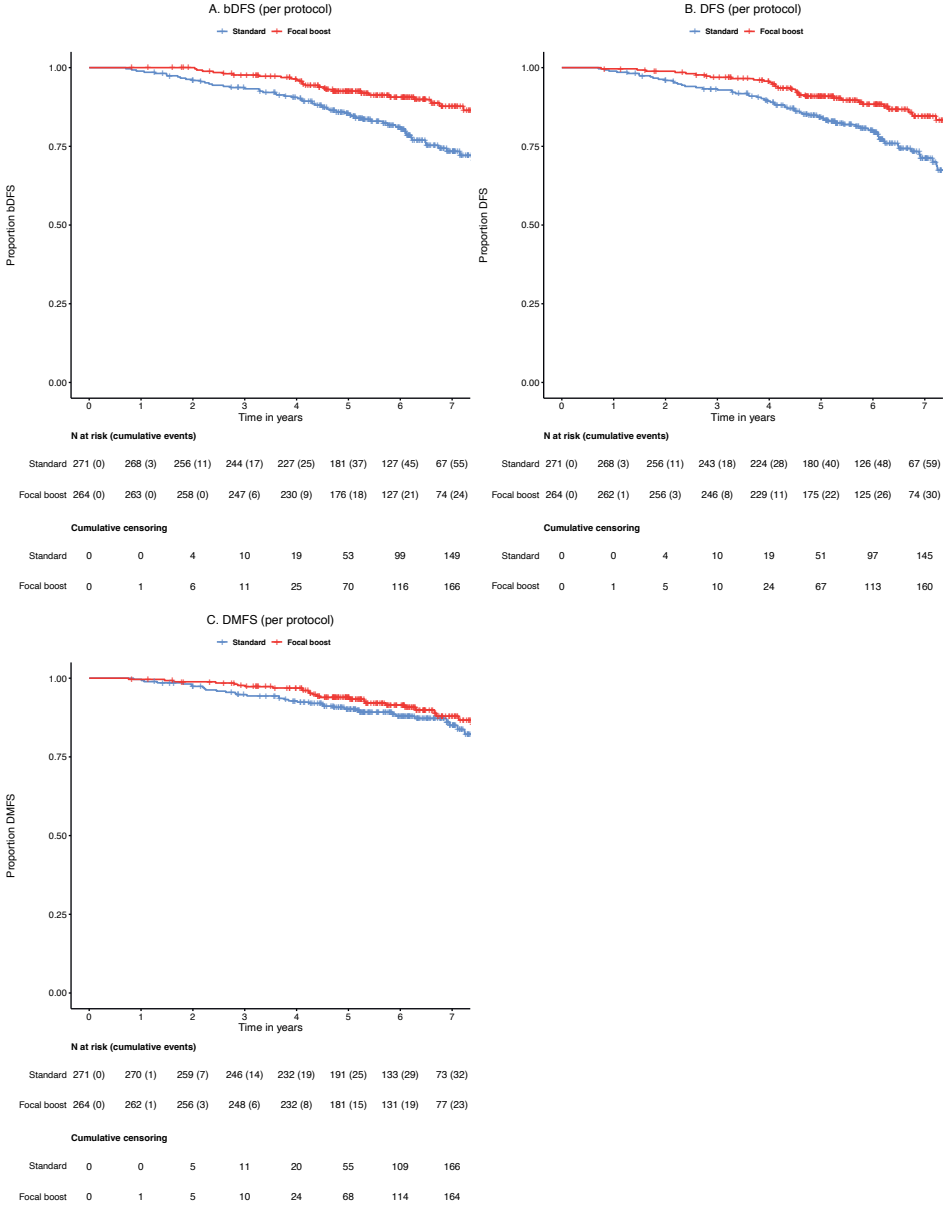



**Figure S2.** Per protocol analysis. Kaplan-Meier curves for biochemical disease-free survival (bDFS) (p<0.001), disease-free survival (DFS) (p<0.001) and distant metastasis-free survival (DMFS) (p=0.25), comparing the standard treatment of 77Gy in 35 fractions to the whole prostate with an additional focal boost to the macroscopic visible tumor up to 95 Gy

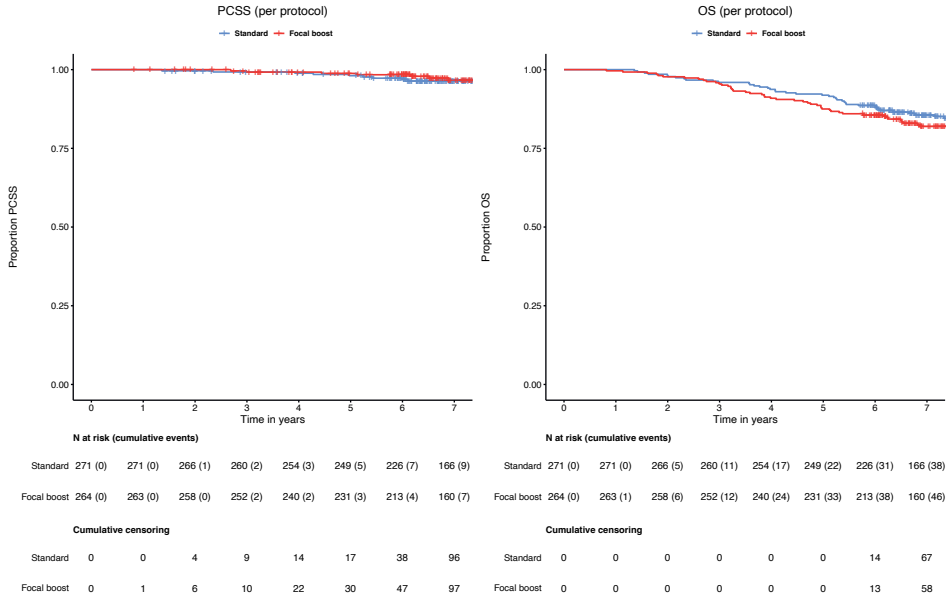



**Figure S3.** Per protocol analysis. Kaplan-Meier curves for prostate cancer-specific survival (PCSS) (p=0.55) and overall survival (OS) (p=0.30) comparing the standard treatment of 77 Gy in 35 fractions to the whole prostate with an additional focal boost to the macroscopic visible tumor up to 95 Gy

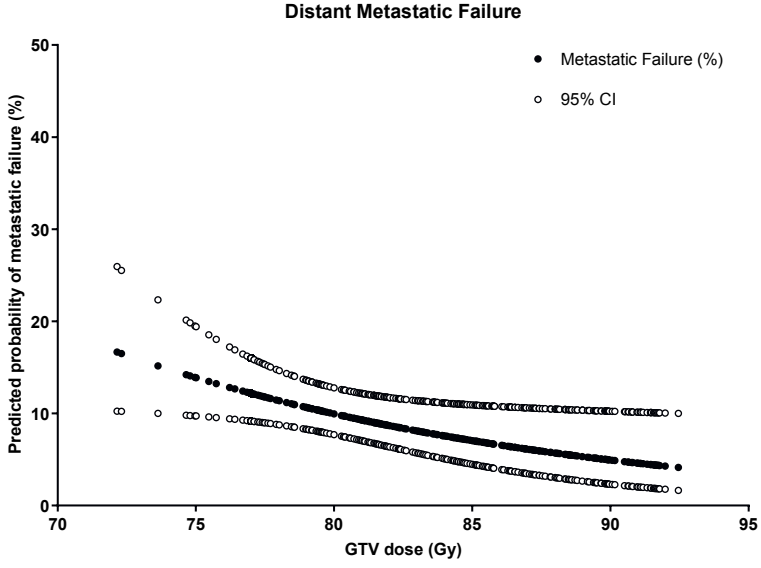
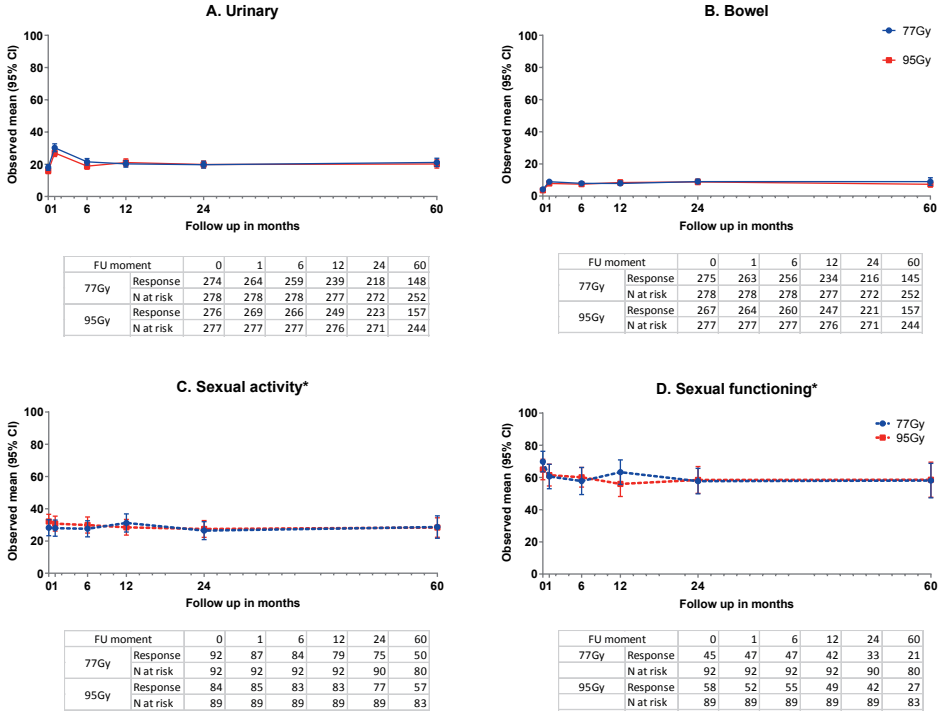



**Figure S4.** Predicted probability of distant metastatic failure up to 7 years as a function of achieved dose to the gross tumor volume (GTV) (D98%; Gy).




| FU moment | | 0 | 1 | 6 | 12 | 24 | 60 |
|---|---|---|---|---|---|---|---|
| 77Gy | Response | 274 | 264 | 259 | 239 | 218 | 148 |
| | N at risk | 278 | 278 | 278 | 277 | 272 | 252 |
| 95Gy | Response | 276 | 269 | 266 | 249 | 223 | 157 |
| | N at risk | 277 | 277 | 277 | 276 | 271 | 244 |

| FU moment | | 0 | 1 | 6 | 12 | 24 | 60 |
|---|---|---|---|---|---|---|---|
| 77Gy | Response | 275 | 263 | 256 | 234 | 216 | 145 |
| | N at risk | 278 | 278 | 278 | 277 | 272 | 252 |
| 95Gy | Response | 267 | 264 | 260 | 247 | 221 | 157 |
| | N at risk | 277 | 277 | 277 | 276 | 271 | 244 |

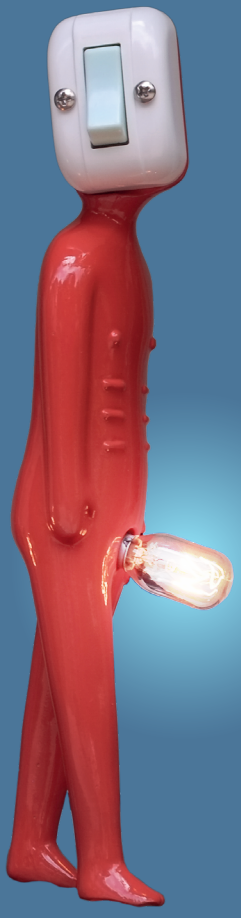
| FU moment | | 0 | 1 | 6 | 12 | 24 | 60 |
|---|---|---|---|---|---|---|---|
| 77Gy | Response | 92 | 87 | 84 | 79 | 75 | 50 |
| | N at risk | 92 | 92 | 92 | 92 | 90 | 80 |
| 95Gy | Response | 84 | 85 | 83 | 83 | 77 | 57 |
| | N at risk | 89 | 89 | 89 | 89 | 89 | 83 |

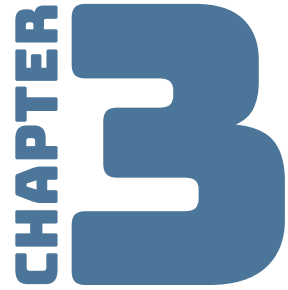
| FU moment | | 0 | 1 | 6 | 12 | 24 | 60 |
|---|---|---|---|---|---|---|---|
| 77Gy | Response | 45 | 47 | 47 | 42 | 33 | 21 |
| | N at risk | 92 | 92 | 92 | 92 | 90 | 80 |
| 95Gy | Response | 58 | 52 | 55 | 49 | 42 | 27 |
| | N at risk | 89 | 89 | 89 | 89 | 89 | 83 |

**Figure S5.** Mean health-related quality of life (HRQoL) (95% CI) per domain over time per treatment arm. Standard treatment of 77 Gy in 35 fractions to the whole prostate versus an additional focal boost to the macroscopic visible tumor up to 95 Gy. Scores for HRQoL range from 0-100. Higher scores indicate more symptoms for the urinary and bowel domains. For sexual activity and sexual functioning lower scores indicate worse symptoms. A difference in score of >5 between both treatment arms was considered clinically relevant.

For HRQoL analysis, 11 patients (n=5 standard treatment; n=6 focal boost) were excluded since no HRQoL data was available.

* Sexual activity and sexual functioning are presented exclusively for patients who did not receive hormonal therapy






# Anorectal dose-effect relations for late gastrointestinal toxicity following external beam radiotherapy for prostate cancer in the FLAME trial

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# ABSTRACT

**Purpose**

The phase III FLAME trial (NCT01168479) showed an increase in five-year biochemical disease-free survival, with no significant increase in toxicity when adding a focal boost to external beam radiotherapy (EBRT) for localized prostate cancer [Kerkmeijer et al. JCO 2021]. The aim of this study was to investigate the association between delivered radiation dose to the anorectum and gastrointestinal (GI) toxicity (grade ≥2).

**Patients and methods**

All patients in the FLAME trial were analyzed, irrespective of treatment arm. The dose-effect relation of the anorectal dose parameters (D2cm$^3$ and D50%) and GI toxicity grade ≥2 in four years of follow-up was assessed using a mixed model analysis for repeated measurements, adjusted for age, cardiovascular disease, diabetes mellitus, T-stage, baseline toxicity grade ≥1, hormonal therapy and institute.

**Results**

A dose-effect relation for D2cm$^3$ and D50% was observed with adjusted odds ratios of 1.17 (95% CI 1.13-1.21, $p < 0.0001$) and 1.20 (95% CI 1.14-1.25, $p < 0.0001$) for GI toxicity, respectively.

**Conclusion**

Although there was no difference in toxicity between study arms, a higher radiation dose to the anorectum was associated with a statistically significant increase in GI toxicity following EBRT for prostate cancer. This dose-effect relation was present for both large and small anorectal volumes. Therefore, further increase in dose to the anorectum should be weighed against the benefit of focal dose escalation for prostate cancer.

## INTRODUCTION

Prostate cancer is the second most common cancer diagnosed in men (1). External beam radiotherapy (EBRT), together with radical prostatectomy, brachytherapy and active surveillance, are standard treatment options for localized prostate cancer (1). Several randomized phase 3 trials have demonstrated that dose escalation ranging from 74 Gy up to 80 Gy of EBRT is feasible and safe with a benefit in biochemical disease-free survival (bDFS) (2-6). The impact on mortality (overall or prostate cancer-specific) is inconclusive. Kuban et al. (2) showed a decrease in prostate cancer deaths in the dose escalation arm. The remaining studies did not find a significant difference in overall or prostate cancer-specific survival between treatment arms (3-6). As whole gland dose escalation leads to increased toxicity (5, 7-10), a further increase in dose to the prostate gland is not desirable. An alternative to improve bDFS without increasing the radiation dose to the organs at risk (OAR) is through a focal boost to the tumor within the prostate (11, 12). The effectiveness and safety of EBRT with a simultaneous integrated boost up to 95 Gy to the macroscopic visible tumor in intermediate- and high-risk prostate cancer patients was studied in the multicenter phase 3 Focal Lesion Ablative Microboost in ProstatE Cancer (FLAME) trial (NCT01168479) (13). After a median follow-up period of five years, a significant increase in bDFS was observed while genitourinary (GU) and gastrointestinal (GI) toxicity rates did not increase (14). Despite predetermined dose-constraints, which were identical in both study arms, regions of the OAR in close proximity to the prostate may have been subjected to a higher radiation dose in the focal boost arm due to the delivered boost to the visible macroscopic tumor. Therefore, the aim of the present study was to analyze the association between absolute (small volume) and relative (large volume) anorectal dose parameters and GI toxicity (grade ≥2) outcomes in patients with localized prostate cancer treated with EBRT in the FLAME trial.

## MATERIAL AND METHODS

**Study design and patient population**

The multicenter, phase 3, single-blinded, randomized controlled FLAME trial compared standard treatment of EBRT for prostate cancer (77 Gy to the prostate) with an experimental arm with an additional integrated boost up to 95 Gy to the macroscopic tumor visible on multiparametric MRI (mpMRI). Participating centers were the University Medical Center Utrecht (UMCU), The Netherlands Cancer Institute (NKI), Radboudumc Nijmegen, The Netherlands, and University Hospitals Leuven, Belgium. The details of the study protocol were described elsewhere (13). Briefly, men with intermediate- and high-risk adenocarcinoma

of the prostate according to the Ash criteria were included in the FLAME trial (15). According to these criteria, men were considered to have intermediate-risk prostate cancer if one of the following factors was present: cT2 carcinoma, Gleason score = 7 or iPSA of 10-20 ng/mL. High-risk prostate cancer was considered when two or more of the aforementioned criteria were present, or if at least one of the following factors was present: ≥cT3a carcinoma, Gleason score 8-10 or iPSA > 20 ng/mL. For further analysis, we used the risk classification according to the European Association of Urology (EAU)(1), as the Ash criteria are no longer used in daily practice.

Patients were excluded if they had a WHO performance score >2, IPSS score ≥ 20, evidence of lymph node involvement or distant metastasis. In addition, patients with a history of prior pelvic radiation, prostatectomy, previous trans urethral resection of the prostate (TURP) within three months prior to radiotherapy, patients without a visible tumor on MRI or who were not able to undergo imaging with an MRI scanner were excluded.

The study was approved by the medical ethics committee of the UMCU, The Netherlands (NL26038.041.08) and of the University Hospitals Leuven, Belgium (B322201110225). Written informed consent was obtained from all included patients.

**Radiotherapy dose and technique**

Patients were randomly assigned to the standard treatment arm or focal boost arm in a 1:1 ratio, stratification for center was performed. Patients in the standard treatment arm were prescribed 77 Gy in 35 fractions of 2.2 Gy to the whole prostate. Patients in the focal boost arm were prescribed an integrated boost up to 95 Gy to the macroscopic tumor, resulting in 35 fractions of 2.7 Gy. Gold fiducial markers were implanted to minimize positioning errors during treatment using an online position verification protocol.

Pre-treatment imaging contained included a CT-scan in treatment position and a mpMRI (including T2-weighted, diffusion-weighted and dynamic contrast-enhanced sequences) for delineation of the target volumes and the OAR.

Delineation of the anorectum was performed from the anus or ischial tuberosities to the recto-sigmoid flexure or sacroiliac joints. The bladder was contoured entirely, from the bladder neck to the bladder dome. The dose prescribed to the planning target volume (PTV) was 77 Gy with a margin of 5-8 mm according to institutional practice. The dose prescribed to the part of the PTV overlapping the rectum and bladder was 70 Gy. There was no clinical target volume (CTV) or PTV margin used for the focal boost. The contouring was performed according to local contouring protocols. Dose-constraints for the anorectum were ≤5%

≥72Gy, ≤50% ≥50 Gy, 1cm3 ≤ 77 Gy. The boost dose up to 95 Gy was as high as could be achieved, respecting the dose-constraints for the OAR. The actual gross tumor volume (GTV) dose therefore varied, based on the patients' anatomy and the location of the GTV(s). Pelvic nodal irradiation was not permitted in the FLAME trial.

**Toxicity assessment**

During treatment, patients were reviewed each week at the treating physician. Follow-up consisted of weekly appointments with the physician during treatment and after treatment at one month, six months, twelve months and yearly thereafter, until a total follow-up time of ten years was reached. Treatment-related toxicity was scored according to CTCAE 3.0 (16) by a physician. The following symptoms were graded and recorded: (peri)rectal pain, proctitis, diarrhea, flatulence, hemorrhoids, fecal incontinence, rectal fistulae and rectal hemorrhage. Cumulative toxicity grade ≥2 was defined as having at least one grade ≥2 event during follow-up. Acute toxicity was defined as GI toxicity grade ≥2 occurring during treatment up to 90 days after start of treatment. Late toxicity was defined as GI toxicity grade ≥2 occurring more than 90 days after start of treatment.

**Statistical analysis**

Anorectal dose parameters and GI toxicity were analyzed irrespective of the randomization arms to make maximal use of the range of the dose to the anorectum within the FLAME trial. We assessed the relation between the dose to the anorectum and GI toxicity grade ≥2 over time. For this study, we focused on the GI toxicity scored by the physician during the first four years of follow-up. An absolute dose-volume parameter ($D2cm^3$), representing the near-maximum dose, was analyzed as parameter of interest since it is less dependent on the volume of the delineated anorectum and has been frequently used in brachytherapy literature (17-19). Additionally, a relative dose parameter (D50%) representing the median dose, was analyzed to be comparable to previous EBRT literature (20-23).

The prevalence of GI toxicity grade ≥2 was plotted graphically over time. The overall cumulative incidence of GI toxicity grade ≥2 and the cumulative incidence of GI toxicity grade ≥2 per separate domain, were calculated based on raw data. To analyze the association between the $D2cm^3$ and D50% of the anorectum and GI grade ≥2 toxicity, generalized linear mixed effect models for dichotomous outcomes were used. To account for a different pattern of GI toxicity over time for acute and late toxicity, we included extra terms to specify differences in the intercept and separate effects (i.e. odds ratios) for time. Furthermore, we adjusted for the accumulating dose during treatment, up to the total planned dose which was delivered after seven weeks (35 fractions).

Unadjusted models only incorporated a dose parameter, the difference between acute and late toxicity and time. The adjusted models also incorporated potential confounding factors: institute, age, T-stage, hormonal therapy, diabetes mellitus, cardiovascular diseases and baseline GI toxicity grade ≥1. The effects of the D2cm$^3$ and D50% dose parameters on the separate GI toxicity complaints were not analyzed, as the power for these analyses is very limited due to low prevalence of toxicity per subdomain. Additionally, the association between acute and late GI grade ≥2 toxicity was assessed separately, using a generalized linear mixed effect model including time and acute GI toxicity grade ≥2 as covariates, with a random intercept for time.

Dose-toxicity curves for the planned dose to D2cm$^3$ and D50% of the anorectum were created. We calculated the cumulative probabilities of GI toxicity for each anorectal dose parameter at each time point based on the regression coefficients from the generalized linear mixed models. These cumulative probabilities were plotted as 'average' in the dose-toxicity curves. As the probabilities vary dependent on the confounding factors, we created risk groups based on baseline patients' characteristics potentially associated with GI toxicity: higher T-stage (T3b or T4), treatment with hormonal therapy, presence of diabetes mellitus, cardiovascular disease and baseline GI toxicity grade ≥1. In the unfavorable risk group, all aforementioned risk factors were present. In the favorable risk group, none of the risk factors were present. These varying cumulative probabilities of GI toxicity were plotted against the dose parameters as range around the average probabilities. More details on the statistical analyses were presented in the Supplementary Material Table S1.

All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and the Statistical Analysis System (SAS) statistical software package, version 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

Of the 571 patients included in the FLAME trial, seven patients were excluded from the analysis of the present study. One patient was diagnosed with concomitant bladder carcinoma for which a cystoprostatectomy was performed. The second patient appeared to have metastasized disease and received hormonal therapy instead of EBRT. The third patient was diagnosed with loco-regional lymph node metastases and received additional pelvic radiation treatment. The remaining four patients were excluded because alternative dose schedules were used. Median follow-up at the time of analysis was 72 months (interquartile range (IQR) 60-84 months).

Patients and treatment characteristics are presented in Table 1. Four patients were excluded for further analysis because of missing rectal dose parameters. The median planned D2cm$^3$ and D50% of the anorectum were 73 Gy (range 59-78 Gy) and 36 Gy (range 3-59 Gy), respectively. With a median planned dose of 73.3 Gy and 73.4 Gy for the D2cm$^3$ and 35.5 Gy and 35.9 Gy for the D50% for the standard treatment arm and focal boost arm respectively, we did not find a statistically significant difference. The distribution of dose parameters is shown in Figure 1. Four years following treatment, the incidence of cumulative acute and late GI toxicity grade ≥2 was 13% and 12%, respectively. The cumulative incidence for grade ≥3 GI toxicity was 1% (n=8). Of these eight patients, two had acute grade ≥3 GI toxicity consisting of rectal hemorrhage. Six patients experienced late grade ≥3 GI toxicity including proctitis (n=1), fecal incontinence (n=1), rectal fistula (n=1) and rectal hemorrhage (n=3).



**Table 1.** Patient and treatment characteristics of the FLAME trial participants at baseline

| **Total number of patients (n)** | | **571** | |
|---|---|---|---|
| **Age (mean, SD)** | | 71 | 6 |
| **iPSA (median, IQR)** | | 11.2 | 7.3-18.5 |
| **Risk classification (EAU) (n, %)** | Low | 6 | 1% |
| | Intermediate | 85 | 15% |
| | High | 480 | 84% |
| **Center (n, %)** | UMC Utrecht | 320 | 56% |
| | UZ Leuven | 93 | 16% |
| | NKI | 109 | 19% |
| | Radboudumc | 49 | 9% |
| **T stage (n, %)** | Missing | 2 | 0% |
| | T1c | 46 | 8% |
| | T2a | 58 | 10% |
| | T2b | 37 | 7% |
| | T2c | 76 | 13% |
| | T3a | 237 | 42% |
| | T3b | 102 | 18% |
| | T4 | 13 | 2% |
| **N stage (n, %)** | Missing | 1 | 0% |
| | N0 | 456 | 80% |
| | pN0 < 10 lymph nodes removed | 81 | 14.% |
| | pN0 ≥ 10 lymph nodes removed | 33 | 6% |
| **M stage (n, %)** | Mx | 143 | 25% |
| | M0 | 428 | 75% |
| **Gleason (n, %)** | < 7 | 103 | 18% |
| | 7 | 276 | 48% |
| | ≥ 8 | 192 | 34% |

**Table 1.** Continued

| **Total number of patients (n)** | | **571** | |
|---|---|---|---|
| **Cardiovascular disease (n, %)** | Missing | 3 | 0% |
| | No | 255 | 45% |
| | Yes | 313 | 55% |
| **Hormonal therapy (n, %)** | Missing | 5 | 1% |
| | No | 190 | 33% |
| | Yes | 376 | 66% |
| **Diabetes mellitus (n, %)** | Missing | 2 | 0% |
| | No | 504 | 89% |
| | Yes | 65 | 11% |
| **Baseline GI toxicity grade ≥1 (n, %)** | No | 526 | 92% |
| | Yes | 45 | 8% |

The prevalence of GI toxicity increased during treatment, normalized one month after treatment, and increased again in the first two years after treatment (Figure 2). We accounted for this evident change in the generalized linear mixed models. The overall cumulative incidence of GI toxicity grade ≥2 and the cumulative incidence of GI toxicity grade ≥2 per separate domain were low (Table 2). The unadjusted odds ratio for developing GI toxicity grade ≥2 was 1.15 (95% CI 1.12-1.19, p<0.0001) for the anorectal $D2cm^3$. An OR of 1.15 means that when the planned dose to the $D2cm^3$ of the anorectum increases with 1 Gy, the odds of developing GI toxicity grade ≥2 increases with 1.15. Adjusted for age, T-stage, hormonal therapy, diabetes mellitus, cardiovascular diseases, baseline GI toxicity grade ≥1 and institute, the odds ratio was 1.17 (95% CI 1.13-1.21, p<0.0001). The unadjusted and adjusted odds ratios for the anorectal D50% for developing GI toxicity grade ≥2 were 1.16 (95% CI 1.12-1.21, p<0.0001) and 1.20 (95% CI 1.14-1.25, p<0.0001), respectively (Table 2). The dose-effect relation is visualized for the average patient including a range from unfavorable to favorable patients in Figure 3.

We carried out a separate model to investigate the association between acute and late GI toxicity and found that acute GI toxicity was associated with late GI toxicity with an OR of 2.58 (95% CI 0.52-12.85, p=0.25).

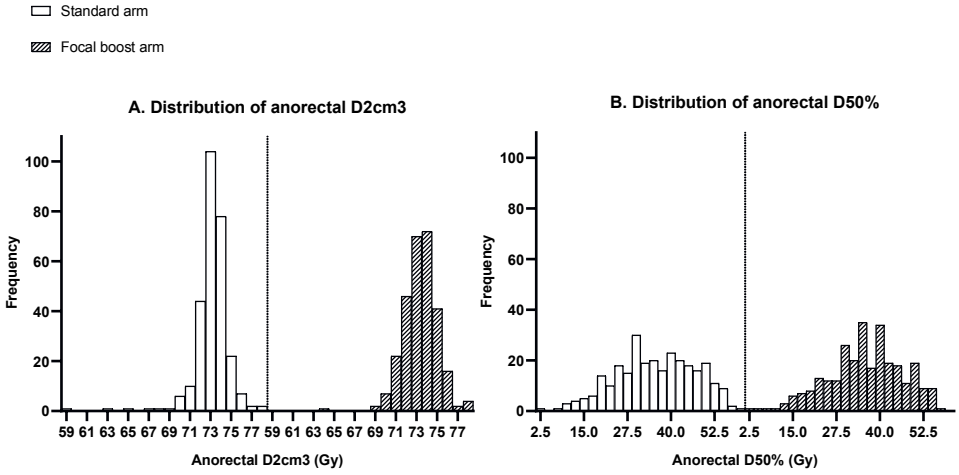
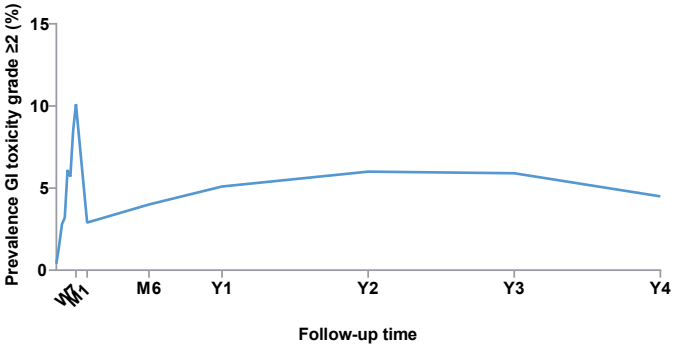



**Figure 1.** Histogram of planned dose to the anorectum per treatment arm. **A.** D2cm$^3$ and **B.** D50%




| FU moment | W7 | M1 | M6 | Y1 | Y2 | Y3 | Y4 |
|---|---|---|---|---|---|---|---|
| % missings | 34 | 15 | 29 | 12 | 21 | 29 | 41 |

*Acute toxicity was defined as W1-7 and month 1
**Late toxicity was defined as M6 and Y1-4

**Figure 2.** Prevalence (%) of observed GI toxicity grade ≥2 per time point (acute* and late** toxicity, effect over time). Missing toxicity values in percentages per time point are shown.

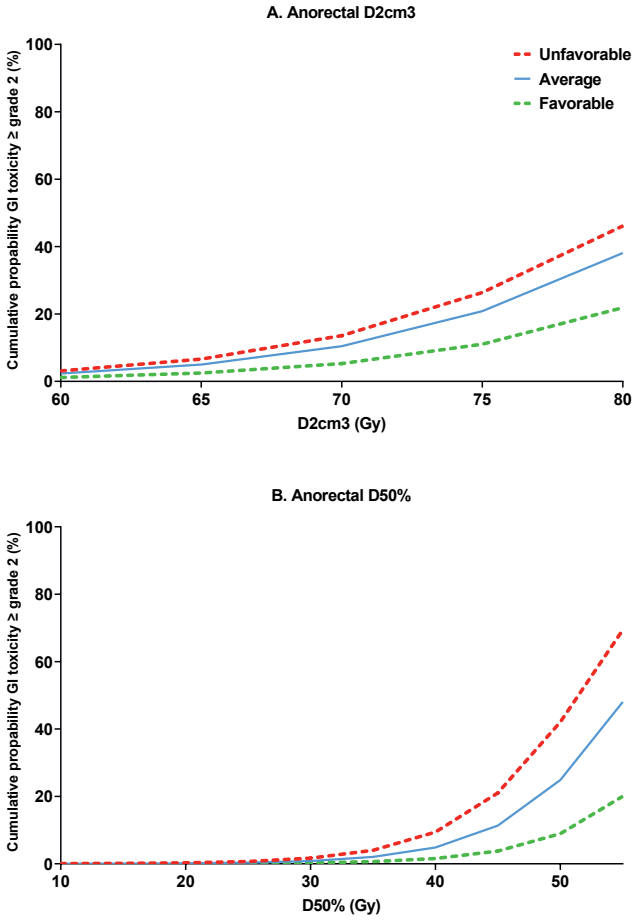



**Figure 3.** Dose-toxicity curves of the probability of late cumulative GI toxicity grade ≥2 related to the planned dose based on the generalized linear mixed effects models adjusted for age, T-stage, hormonal therapy, diabetes mellitus, cardiovascular diseases, baseline GI toxicity grade ≥1 (average probability of GI toxicity) and institute. The risk groups are based on baseline patient characteristics potentially associated with GI toxicity. In the unfavorable risk group, all aforementioned risk factors were present. In the favorable risk group, none of the risk factors were present. A. D2cm$^3$ (Gy) and B. D50% (Gy).

## DISCUSSION

In this study, we analyzed the effect of anorectal radiation dose on GI toxicity in localized prostate cancer patients treated with EBRT using data from the FLAME trial. We found a dose-effect relation between anorectal radiation dose (D2cm$^3$ and D50%) and GI toxicity grade ≥2, with higher doses leading to higher odds of GI toxicity.

The primary analyses of the FLAME trial showed that the addition of a focal boost to EBRT in patients with localized prostate cancer resulted in a significantly increased five-year bDFS. As focal boosting may become the new standard of care, rectal dose constraints and anorectal dose-effect relations become of increasing importance. We previously showed that there is no statistically significant or clinically relevant difference in GI toxicity and patient-reported quality of life at five-year follow-up between the treatment arms of the FLAME trial (14). This result must be attributed to the strict adherence to the dose constraints for the anorectum, prioritizing organ at risk constraints over the focal boost dose (24). The absence of a statistically significant increase in toxicity should not be interpreted as an absence of a dose-effect relation for GI toxicity, as we indeed found in this study.

In line with the present findings, Storey et al. (MD Anderson whole-gland dose escalation trial, 70 Gy vs. 78 Gy in 2 Gy/fraction) observed a significant association between the volume of the rectum irradiated to ≥70 Gy and long-term rectal complications. They concluded that further increasing the dose (>78 Gy) to the entire prostate, would require smaller margins to prevent increasing GI toxicity (25). In addition, Gulliford et al. (the MRC RT01 whole-gland dose escalation trial, 64 Gy vs 74 Gy in 2 Gy/fraction) observed a relation between an increase in volume at specific dose levels to the rectum and late rectal toxicity (26).

A similar observation was seen in hypofractionation trials for localized prostate cancer, suggesting that increased intermediate- (V30-V40) and high- (D5%, Dmax) dose volumes of the rectum were associated with increased late GI toxicity (27, 28). Additionally, associations with intermediate-high dose regions (30 to 50 Gy) and separate GI toxicity endpoints were observed (29, 30). Notably, hypofractionated dose schemes and conventionally fractionated schemes should be compared with caution, as no consensus is reached on how dose-effect relation models should be adjusted for fractionation scheme changes, especially with high doses per fraction (31, 32).

The selection of dose parameters (D2cm$^3$, D50%) might have influenced the results of the dose-effect relation analysis. For this study, the D2cm3 was considered to be the most relevant parameter to include in the analysis, since it resembles the high dose region and has been frequently used in brachytherapy literature. The D2cm$^3$ is expected to be most sensitive for the focal boost dose. The length of the anorectum contoured does not influence the D2cm$^3$ volume in the radiotherapy plan (23). The anorectal D50% was chosen because of the middle dose region it resembles, possibly covering another type of dose-effect relation. The models that we have created are specifically based on dose-parameters with units in Gray. We did not include relative dose-parameters with units in percentages.

The first limitation of our study is, the whole anorectum was analyzed, as the anal canal, rectal wall, rectum and anorectum were not contoured separately. There were no specific contouring guidelines that were followed. Prior to our analyses we checked the delineations of the anorectum per treating center in order to make sure that potential inconsistencies were not going to affect our analysis. Delineations that did not meet our expectations, specifically in length directions, were adjusted to ensure similar delineated volumes of the anorectum. In the multivariable analyses we corrected for any remaining systematic differences between treating centers by correcting for center.

Secondly, there was a considerable amount of missing toxicity data. A generalized linear mixed effect model with random effects to determine the rectal dose-effect relations was used to cope with this limitation. In addition to handling both single and recurring toxicity occurrence, these models provide unbiased estimations in the presence of missing data under the missing-at-random assumption (33). Though we have no reason to doubt this assumption, missing-at-random is essentially unverifiable. Missing data is inherent to a clinical trial with a follow-up duration of ten years. We believe that by using a longitudinal approach within a generalized linear mixed effect model with random effects to determine the rectal dose–effect relations, the influence of missing data on our findings is minimized.

Since the FLAME trial showed an increased five-year bDFS, when adding a focal boost (14), further optimization of the treatment plans in order to increase the boost to the tumor without increasing the dose to the anorectum, should be a focus for future research.

In conclusion, a dose–effect relation between the anorectal radiation dose and GI toxicity grade ≥2 was observed, with higher doses leading to higher risk of GI toxicity. The range in anorectal dose in the FLAME trial was limited due to strict anorectal dose constraints that were identical for the standard arm and focal boost arm. Nevertheless, even in the small range of dose variation for both small ($D2cm^3$) and large anorectal volumes (D50%), a significant dose–effect relation between anorectal dose parameters and GI toxicity was observed.

Further increasing the anorectal dose should be weighed against the benefit of focal boosting and optimization of current (focal) dose escalation strategies without increasing the anorectal dose should be explored. Besides focal dose escalation strategies, extreme hypofractionation and online adaptive radiotherapy with reduced PTV margins may further decrease the biologically effective dose and irradiated volume of the anorectum, reducing the risk of toxicity.

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# SUPPLEMENTARY MATERIAL

**Table S1.** Stepwise detailed description of statistical analyses:

| **Step 1: Available toxicity data** |
|---|
| Toxicity data was collected by a physician in the four participating centers. The CTCAE 3.0 score was taken weekly during treatment and at one month, six months and yearly thereafter up to ten years. Inherent to a trial with a total follow-up duration of ten years, we had a substantial amount of missing toxicity data. Missing toxicity data percentages per measured time point were comparable between the treatment arms. |
| **Step 2: The implementation of generalized linear mixed effect models** |
| A generalized linear mixed effect model with random effects to determine the rectal dose-effect relations for GI toxicity grade ≥2 was used. Generalized linear mixed effect models include all available data without excluding subjects with missing follow-up data. With the use of a likelihood-based estimation method, the missing values are estimated based on the existing data [1] under the missing-at-random (MAR) assumption. Although we cannot verify whether the toxicity data was MAR [2,3], we have no reason to doubt this assumption. |
| **Step 3: Fixed and random effects included in model** |
| Fixed effects:<br>*Timediff (dichotomous: acute versus late toxicity)*<br>*Timediff*Time (weeks)*<br>*Institute*<br>*Cardiovascular disease*<br>*Diabetes mellitus*<br>*Baseline GI toxicity grade ≥1*<br>*Age*<br>*Accumulating dose**<br>*T-stage*<br>*Hormonal therapy*<br><br>Random effects: intercept and random slope for Timediff*time, with *Patient ID* as a subject.<br><br>In the analysis, we excluded an overall intercept thereby effectively incorporating a separate intercept for acute and late toxicity. Furthermore, by incorporating the Timediff*time interaction, we allowed for different time effects for acute and late toxicity**. Ideally, random effects should be estimated separately for the intercept and time effects for acute and late toxicity.<br><br>**Accumulating dose during treatment = dose-parameter * (time in weeks/7) for the first seven weeks, the full dose was used thereafter*<br>*** An example for this kind of parametrization (albeit a very different application) can be found in the SAS manual: https://documentation.sas.com/doc/en/pgmsascdc/9.4_3.4/statug/statug_glimmix_examples08.htm* |
| **Step 4: Creating dose-effect curves** |
| The estimated probability of GI toxicity grade ≥2 was calculated for the rectal D2cm3 with a dose range of 60-80Gy in steps of 5Gy. For the rectal D50%, the estimated probability of GI toxicity grade ≥2 was calculated with a dose range of 10-55 Gy in steps of 5 Gy.<br><br>To model the dose-effect curve for the average patient we used the prevalence of the risk factors within our cohort. The risk factors were selected based on the available data, literature and physicians experience. A history of cardiovascular disease, diabetes mellitus, a higher T-stage, the prescription of hormonal therapy and the presence of baseline GI toxicity grade 1 were considered to be risk factors for increased toxicity. |

**Table S1.** Continued

| **Step 4: Creating dose-effect curves** |
|---|
| Although it is not shown in literature that hormonal therapy in combination with radiotherapy increases late GI toxicity [4], hormonal therapy was included in the multivariable model, to adjust for its potential influence on the dose-effect relation of the rectal dose and GI toxicity. Shadad et al. [5] suggested that patients with vascular diseases and diabetes mellitus are prone to increased late treatment related GI and GU toxicity. A higher T-stage was considered to be of greater risk for developing GI toxicity, since a higher T-stage could lead to a larger part of the rectum to be exposed to a higher radiation dose. Baseline GI toxicity is known to be a risk factor for radiation induced late GI toxicity and was included in the model.<br><br>Given the dose to the rectal dose parameter, the estimated probability of experiencing GI toxicity grade ≥2 for an average patient having 55% cardiovascular disease, 11% diabetes mellitus, 66% hormonal therapy, baseline GI toxicity grade ≥1 of 9% and a T-stage with a prevalence of 24% T1c,T2a, T2b combined, T2c 13%, T3a of 42% and T3b, T4 combined of 20% was calculated<br><br>To model the dose-effect curve for a favorable patient, we created a patient with none of the risk factors above present. We calculated the estimated probability of experiencing GI toxicity grade ≥2 for a patient having 0% cardiovascular disease, 0% diabetes mellitus, 0% hormonal therapy, 0% baseline GI toxicity and the presence of T1c, T2a or T2b.<br><br>To model the dose-effect curve for an unfavorable patient we created a patient with all of the risk factors above present. We calculated the estimated probability of experiencing GI toxicity grade ≥2 for a patient having 100% cardiovascular disease, 100% diabetes mellitus, 100% hormonal therapy, 100% baseline GI toxicity and the presence of T3b or T4.<br><br>The creation of the (un) favorable dose-effect curves was based on literature and represent the most extreme ranges for GI toxicity possible: a patient with none of the potential risk factors present versus a patient with all potential risk factors present.<br><br>In reality, all men with prostate cancer who will be treated with external beam radiotherapy according to the FLAME treatment schedule, will have an estimated probability of GI toxicity grade ≥2 that will lie within the range that we provided with our dose-effect curves. |

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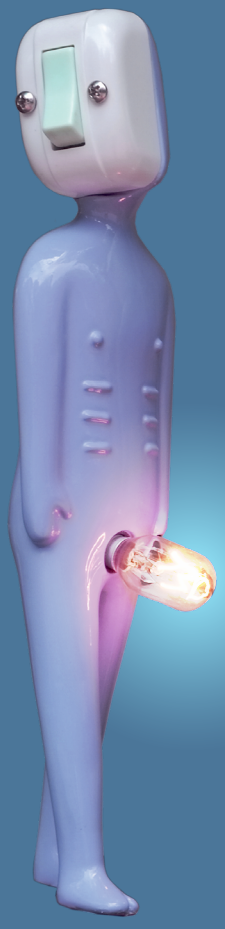

CHAPTER 4

# Urethral and bladder dose-effect relations for late genitourinary toxicity following external beam radiotherapy for prostate cancer in the FLAME trial

*Radiotherapy & Oncology*

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## ABSTRACT

**Purpose**

The FLAME trial (NCT01168479) showed that by adding a focal boost to conventional fractionated EBRT in the treatment of localized prostate cancer, the five-year biochemical disease-free survival increased, without significantly increasing toxicity. The aim of the present study was to investigate the association between radiation dose to the bladder and urethra and genitourinary (GU) toxicity grade ≥2 in the entire cohort.

**Patients and methods**

The dose-effect relations of the urethra and bladder dose, separately, and GU toxicity grade ≥2 (CTCAE 3.0) up to five years after treatment were assessed. A mixed model analysis for repeated measurements was used, adjusting for age, diabetes mellitus, T-stage, baseline GU toxicity grade ≥1 and institute. Additionally, the association between the dose and separate GU toxicity subdomains were investigated.

**Results**

Dose-effect relations were observed for the dose (Gy) to the bladder D2cm$^3$ and urethra D0.1cm$^3$, with adjusted odds ratios of 1.14 (95% CI 1.12-1.16, p<0.0001) and 1.12 (95% CI 1.11-1.14, p<0.0001), respectively. Additionally, associations between the dose to the urethra and bladder and the subdomains urinary frequency, urinary retention and urinary incontinence were observed.

**Conclusion**

Further increasing the dose to the bladder and urethra will result in a significant increase in GU toxicity following EBRT. Focal boost treatment plans should incorporate a urethral dose-constraint. Further treatment optimization to increase the focal boost dose without increasing the dose to the urethra and other organs at risk should be a focus for future research, as we have shown that a focal boost is beneficial in the treatment of prostate cancer.

# INTRODUCTION

Whole-gland dose escalation up to 80 Gy to the entire prostate has shown to be effective regarding biochemical disease-free survival (bDFS) in the treatment of prostate cancer (1-5). However, further increasing the dose to the entire prostate using external beam radiotherapy (EBRT) often results in higher genitourinary (GU) and gastrointestinal (GI) toxicity because of an increased dose to the surrounding organs at risk (OAR) (4, 6-9). Instead of further increasing the dose to the entire prostate, the phase 3 multicenter randomized controlled Focal Lesion Ablative Microboost in ProstatE cancer (FLAME) trial (NCT01168479) compared effectiveness and toxicity of EBRT with and without a simultaneous integrated focal boost up to 95 Gy to the macroscopic tumor(s) in intermediate- and high-risk localized prostate cancer patients (10). The addition of a focal boost to conventionally fractionated EBRT significantly increased the five-year bDFS. With strict adherence to the dose-constraints of the bladder and without a urethral dose-constraint, differences in cumulative GU toxicity rates were small and not statistically significant between the treatment arms of the FLAME trial (11, 12). The development of GU toxicity is multifactorial and originates from clinical risk factors and irradiated volumes of the bladder and the urethra (13-15). Dosimetry studies addressing the association between GU toxicity and urethral dose parameters based on large whole-gland dose escalation trials are scarce because of the invisibility of the urethra on computed tomography (CT) scans, which were commonly used for the radiotherapy planning (16). When Magnetic Resonance Imaging (MRI) is used for contouring of the target volume and OAR, it is possible to delineate the urethra and carry out dose-effect relation analyses for the urethral dose in correlation with GU toxicity.



By adding a focal boost dose to whole-gland EBRT, an inhomogeneous dose to the prostate was given. This inhomogeneous dose allows to differentiate between the dose to the bladder and urethra. Moreover, in the FLAME trial, we did not use a urethral dose-constraint in treatment planning. This resulted in a significant heterogeneity in the dose to the urethra, allowing us to perform a dose-effect analysis with a wide dose range for the urethra. The objective of this study was to perform a dose-effect relation analysis for the urethral and bladder dose parameters and GU toxicity grade ≥2 in patients with localized prostate cancer treated with EBRT in the FLAME trial in the study cohort, irrespective of randomization arm.

## MATERIAL AND METHODS

**Study design and patient population**

In the FLAME trial, standard whole-gland EBRT was compared to an additional simultaneous integrated focal boost up to 95 Gy for localized prostate cancer. The University Medical Center Utrecht (UMCU), The Netherlands Cancer Institute (NKI), Radboudumc Nijmegen in The Netherlands and University Hospitals Leuven in Belgium were participating centers.
Patients with intermediate- and high-risk prostate cancer according to the Ash criteria (17) were included. Patients were excluded if they had a WHO performance score >2, IPSS score ≥20, evidence of lymph node involvement or distant metastasis, history of prior pelvic irradiation, prostatectomy or trans urethral resection of the prostate (TURP) within three months prior to radiotherapy. Additionally, patients who could not undergo MRI, or patients with an undefinable tumor on MRI were excluded.
Approval was given by the medical ethics committee of the UMCU, The Netherlands (NL26038.041.08) and of the University Hospitals Leuven, Belgium (B322201110225). All included patients gave written informed consent.

**Radiotherapy dose and technique**

Patients were randomized between the standard arm (77 Gy in 35 fractions of 2.2 Gy to the whole prostate, during seven weeks) and the focal boost arm in a 1:1 ratio, with stratification per center. Patients in the focal boost arm received an additional simultaneous integrated boost to the macroscopic tumor up to 95 Gy, resulting in 35 fractions of 2.7 Gy. In order to reduce positioning errors, gold fiducial markers were implanted. Conventional linear accelerators were used to carry out either intensity-modulated radiotherapy or volumetric modulated arc therapy. For delineation of the target volumes and OAR, CT-scans and multiparametric mpMRI-scans with T2-weighted, diffusion-weighted and dynamic contrast-enhanced images were acquired. The boost dose to the gross tumor volume (GTV) in the focal boost arm varied between patients, as the dose-constraints to the OAR were prioritized over the focal boost dose. The planning target volume (PTV) was prescribed 77 Gy with a margin of 5-8 mm around the clinical target volume (CTV), depending on the participating center. The part of the PTV overlapping the rectum and bladder was prescribed 70 Gy. There was no margin around the GTV.

The entire bladder was contoured, from the bladder neck to the bladder dome. Dose-constraints to the bladder were: V72Gy < 10% and D1cm$^3$ <80 Gy. Bladder filling protocols differed per participating centre, patients were generally advised to have a comfortably filled bladder during planning CT, MRI and treatment. There was no dose-constraint for the urethra used for treatment planning. Therefore, to allow for the present dose-effect relation

analysis, the urethra was contoured in all patients using the sagittal and axial images of the T2-weighted turbo spin echo (TSE) sequence. The prostatic urethra was delineated using a circle shape with 6 mm diameter. After delineation of the urethra, cumulative dose-volume histograms (DVHs) were calculated. Absolute dose parameters that represent the near maximum dose (bladder $D2cm^3$, urethra $D0.1cm^3$) were used, because these are considered to be most susceptible to the focal boost dose.

**Toxicity assessment**

Patients were reviewed weekly by the physician during treatment. After treatment, follow-up consisted of appointments with the physician at one month, six months, twelve months and yearly thereafter up to ten years. Treatment-related toxicity was scored using the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. GU toxicity endpoints were: urinary frequency, retention, bladder spasm, incontinence, hematuria and dysuria. For the CTCAE 3.0, scores ranged from zero to grade five toxicity.



**Statistical analysis**

In this paper, we investigated the dose to the urethra and bladder, separately, in relation to GU toxicity grade ≥2, irrespective of the treatment arms. Generalized linear mixed effect models were used to assess the association between the dose parameters and GU toxicity over time. The cumulative incidence of toxicity was calculated as the number of patients that experienced any event of grade ≥2 GU toxicity at some point after radiotherapy.
The different rates of acute GU toxicity (up to 90 days after start of treatment) and late GU toxicity (from 90 days after start of treatment up to five years) was accounted for with a separate intercept and a separate effect for time for acute and late toxicity. To account for multiple measurements per patient, we included a random effects intercept and a random effect for time. We accounted for the increasing dose during treatment up to seven weeks (35 fractions), and used the total planned dose thereafter. We adjusted the models for age, baseline GU toxicity grade ≥1, diabetes mellitus, T-stage and institute (fixed effects).
The associations of the dose and urinary frequency, urinary retention and urinary incontinence were assessed without adjusting for potential confounders, because of the low number of toxicity events per subdomain. The endpoints hematuria and dysuria were considered to have too few events per measured time point and were not separately analyzed.

Dose-toxicity curves were created based on the estimated probabilities of late GU toxicity and the planned dose to the bladder $D2cm^3$, and the $D0.1cm^3$ of the urethra. Probabilities for developing late GU toxicity were calculated based on the average patient. As a range around the average patient curve, we plotted the probability of developing late GU toxicity

in an unfavorable risk group in which all potential risk factors for GU toxicity (higher T-stage (T3b or T4), diabetes mellitus and baseline GU toxicity grade ≥1) were present, and a favorable risk group in which none of the aforementioned risk factors were present, with a mean age of 71 years old. In addition, we analyzed the effect of acute GU toxicity on late GU toxicity in a generalized linear mixed effect model, adjusted for age, baseline GU toxicity grade ≥1, diabetes mellitus, T-stage and institute. Additional information on the statistical analyses were presented in the supplementary material Table S1.

All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

At time of the present analysis, all 571 patients had potentially reached five years of follow-up, with a median follow-up of 72 months (interquartile range (IQR) 58-86). Baseline characteristics are presented in Table 1. The mean age at time of randomization was 71 years (SD 6). For further analysis, 91 patients were excluded. Three patients were excluded because they received a different type of treatment than originally planned: one patient was treated with hormonal treatment alone because of metastatic disease on the planning CT/MRI scans, another patient received additional pelvic radiotherapy because of positive lymph nodes and the third patient underwent a cystoprostatectomy, as he was diagnosed with concomitant bladder carcinoma. Another ten patients without dosimetry data available and 78 patients who underwent a previous TURP were excluded.

For the present study we addressed the GU toxicity up to five years. The cumulative acute and late GU toxicity rates grade ≥2 are presented in Table 2. Cumulative acute toxicity grade ≥3 was seen in 3% (n=18) of the patients, including urinary frequency (n=9), urinary obstruction (n=8), urinary incontinence (n=1) and dysuria (n=1). Cumulative late toxicity grade ≥3 was seen in 5% (n=27) of the patients, including urinary frequency (n=5), urinary obstruction (n=11), urinary incontinence (n= 7), bladder spasm (n=1), hematuria (n=6) and dysuria (n=2). Grade 4 GU toxicity occurred in one patient, who required a permanent urinary diversion due to severe incontinence, three years after treatment. Urethral strictures occurred in 18 patients (4%), requiring medical interventions including urethral dilatation, urethrotomy or daily intermittent self-catheterization. Over half of the strictures (13/18) occurred more than two years after treatment. In one patient a cystectomy including a partial prostatectomy was required four years after radiotherapy, because of urethral necrosis following a urethrotomy earlier that year. We did not determine the location of the urethral strictures.

**Table 1.** Patient and treatment characteristics of the FLAME trial participants at baseline

| **Total number of patients (n)** | | 571 | |
|---|---|---|---|
| **Age in years (mean, SD)** | | 71 | 6 |
| **iPSA ng/mL (median, IQR)** | | 11.2 | 7.3-18.5 |
| **Risk classification (EAU) (n, %)** | Low | 6 | 1% |
| | Intermediate | 85 | 15% |
| | High | 480 | 84% |
| **Center (n, %)** | UMC Utrecht | 320 | 56% |
| | UZ Leuven | 93 | 16% |
| | NKI | 109 | 19% |
| | Radboudumc | 49 | 9% |
| **T stage (n, %)** | Missing | 2 | 0% |
| | T1c | 46 | 8% |
| | T2a | 58 | 10% |
| | T2b | 37 | 7% |
| | T2c | 76 | 13% |
| | T3a | 237 | 42% |
| | T3b | 102 | 18% |
| | T4 | 13 | 2% |
| **N stage (n, %)** | Missing | 1 | 0% |
| | N0 | 456 | 80% |
| | pN < 10 lymph nodes removed | 81 | 14.% |
| | pN ≥ 10 lymph nodes removed | 33 | 6% |
| **M stage (n, %)** | Mx | 143 | 25% |
| | M0 | 428 | 75% |
| **Gleason (n, %)** | < 7 | 103 | 18% |
| | 7 | 276 | 48% |
| | ≥ 8 | 192 | 34% |
| **Cardiovascular disease (n, %)** | Missing | 3 | 0% |
| | No | 255 | 45% |
| | Yes | 313 | 55% |
| **Hormonal therapy (n, %)** | Missing | 5 | 1% |
| | No | 190 | 33% |
| | Yes | 376 | 66% |
| **Diabetes mellitus (n, %)** | Missing | 2 | 0% |
| | No | 504 | 89% |
| | Yes | 65 | 11% |
| **Baseline GU toxicity (n, %)** | Missing | 16 | 3% |
| | No | 356 | 62% |
| | Grade 1 | 147 | 26% |
| | Grade 2 | 46 | 8% |
| | Grade 3 | 6 | 1% |
| | Grade 4 | NA | NA |
| | Grade 5 | NA | NA |

Abbreviations:
SD=standard deviation, iPSA=initial prostate specific antigen, IQR=interquartile range, EAU=European Association of Urology, T stage= T refers to the size and extent of the main tumor, N stage = N refers to the number of nearby lymph nodes that have cancer, M stage= M refers to whether the cancer has metastasized, GU = genitourinary.

The median planned dose to the D2cm$^3$ of the bladder and the D0.1cm$^3$ of the urethra were 75 Gy (IQR (74-76) and 80 Gy (IQR 78-87), respectively, see Figure 1 for the dose distributions per treatment arm. For the bladder D2cm$^3$ we found a dose-effect relation with an unadjusted odds ratio of 1.15 (95% CI 1.13-1.17, p<0.0001). This means that when the planned dose to the D2cm$^3$ of the bladder increases with 1 Gy, the odds of developing GU toxicity grade ≥2 increases with 1.15. Adjusted for age, T-stage, diabetes mellitus, baseline GU toxicity grade ≥1 and institute, the odds ratio was 1.14 (95% CI 1.12-1.16, p<0.0001). The odds ratios for the urethra D0.1cm$^3$ for developing GU toxicity grade ≥2 were 1.13 (95% CI 1.11-1.15, p<0.0001) and (after adjustment for confounders) 1.12 (95% CI 1.11-1.14, p<0.0001) per increase of 1 Gy (Table 2).

These associations were visualized as dose-effect curves for the average patient, and for unfavorable and favorable risk groups based on patient characteristics in Figure 2. When using a cut-off for the dose to the urethra of 80 Gy, cumulative toxicity rates were 22.3% (58/260) and 26.4% (58/220), respectively.
The dose-effect relations of the GU toxicity subdomains are presented in Table 2. For the endpoints urinary retention and urinary incontinence the random effect for time was excluded, since the corresponding covariance parameter estimates were zero. An additional generalized linear mixed effect model showed that acute GU toxicity was associated with late GU toxicity with an adjusted odds ratio of 5.82 (95% CI 1.65-20.56, p=0.006).

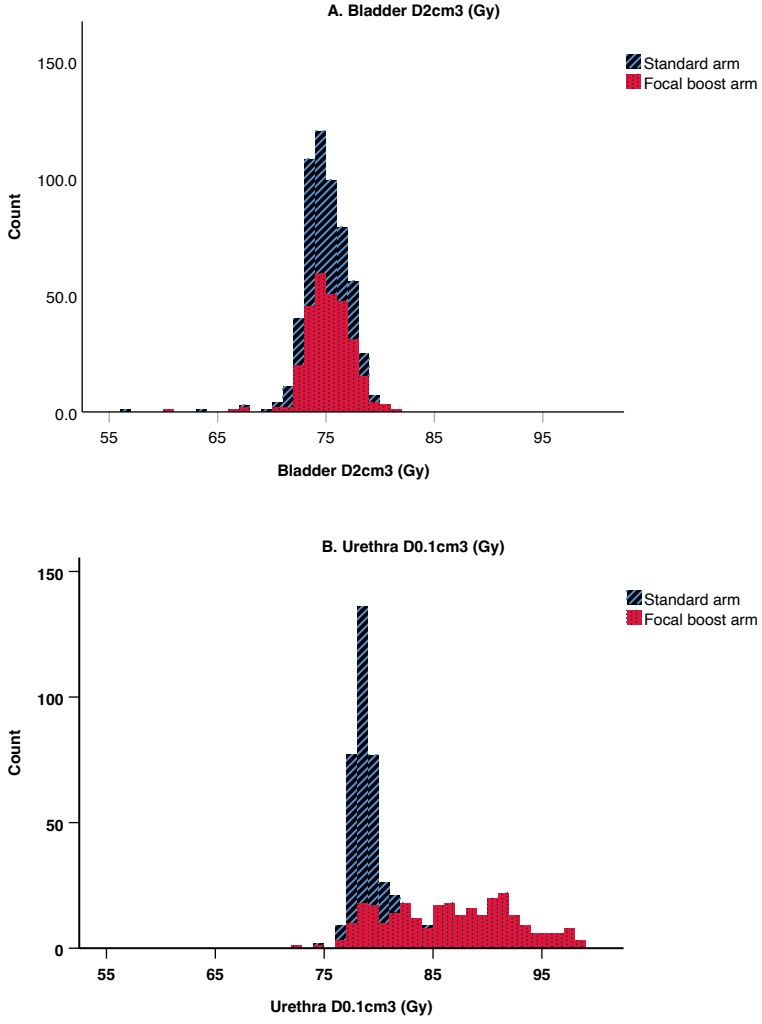


**Figure 1.** Stacked histogram of planned dose (Gy) to the A. bladder D2cm$^3$ (standard arm and focal boost arm, median 75 Gy (IQR 74-76) and 75 Gy (IQR 74-77), respectively) and B. urethra D0.1cm$^3$ (standard arm and focal boost arm, median 78 Gy (IQR 78-79) and 86 Gy (IQR 82-91), respectively) per treatment arm. Abbreviations: IQR=interquartile range

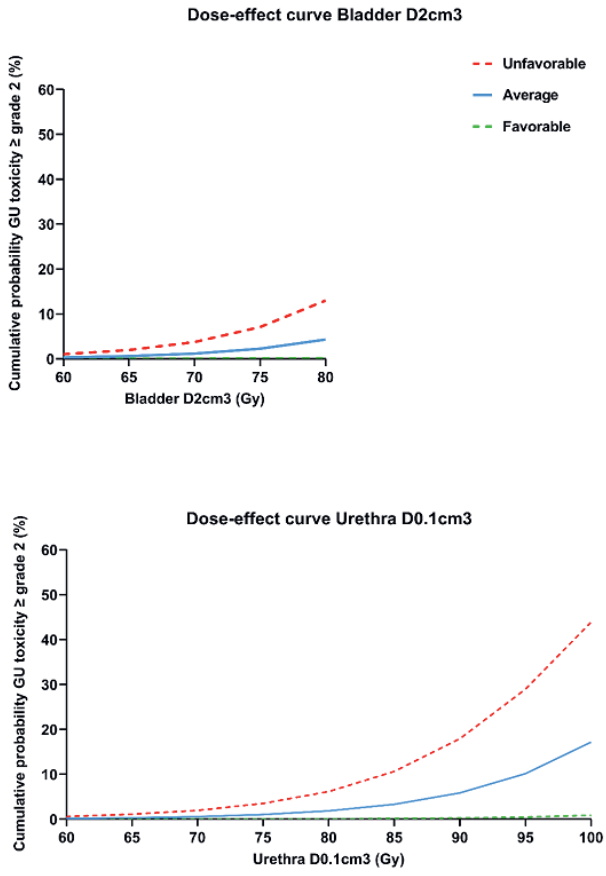


**Figure 2.** Dose-toxicity curves of the average and (un)favorable estimated cumulative GU toxicity grade ≥2, related to the planned dose based on the generalized linear mixed effects models adjusted for age, T-stage, diabetes mellitus, baseline GU toxicity grade ≥1. The risk groups are based on baseline patient characteristics potentially correlated with GU toxicity. In the unfavorable risk group, all aforementioned risk factors were present. In the favorable risk group, none of the risk factors were present. A. bladder D2cm$^3$ (Gy) and B. urethra D0.1cm$^3$ (Gy).
Abbreviations: GU=genitourinary, T-stage= T refers to the size and extent of the main tumor

**Table 2.** The association between urethra and bladder dose and cumulative GU toxicity: results of generalized linear mixed models with and without adjustment for potential confounding factors for GU toxicity. Results for late cumulative GU toxicity grade ≥2 and late separate GU toxicity grade ≥2 endpoints are shown.

| **Total n=480** | **Overall GU toxicity grade ≥2** | | **Urinary frequency grade ≥2** | **Urinary retention grade ≥2** | **Urinary Incontinence grade ≥2** | **Hematuria grade ≥2** | **Dysuria grade ≥2** |
|---|---|---|---|---|---|---|---|
| **Acute* cumulative toxicity** | 47% (95% CI 42-51%, n=225) | | 37% (95% CI 33-42%, n=179) | 15% (95% CI 12-19%, n=74) | 3% (95% CI 2-5%, n=13) | 0% (95% CI 0-1%, n=1) | 5% (95% CI 3-7%, n=23) |
| **Late* cumulative toxicity** | 24% (95% CI 21-28%, n=116) | | 16% (95% CI 13-19%, n=75) | 8% (95% CI 6-11%, n=39) | 5% (95% CI 4-8%, n=26) | 1% (95% CI 1-3%, n=6) | 2% (95% CI 1-3%, n=8) |
| | **Unadjusted OR (95% CI)** | **Adjusted OR (95% CI)** | | | **Unadjusted OR (95% CI)** | | |
| **Bladder D2cm³** | 1.15 (1.13 1.17, p<0.0001) | 1.14 (1.12 1.16, p<0.0001) | 1.17 (1.15 1.20, p<0.0001) | 1.17 (1.13 1.22, p<0.0001) | 1.12 (1.05 1.20, p=0.001) | | |
| **Urethra D0.1cm³** | 1.13 (1.11 1.15, p<0.0001) | 1.12 (1.11 1.14, p<0.0001) | 1.15 (1.13 1.17, p<0.0001) | 1.15 (1.11 1.18, p<0.0001) | 1.11 (1.05 1.18, p<0.001) | | |

The ORs for the dose-parameters mean that when the planned dose to the urethra and bladder increases with 1Gy, the odds of developing GU toxicity grade ≥2 increase with the corresponding given OR.
* Acute toxicity was defined as toxicity from the start of treatment up to 90 days, late toxicity was defined as from 90 days after start of treatment up to five years after treatment
Abbreviations: GU=genitourinary, CI=confidence interval, OR=odds ratio

## DISCUSSION

Although cumulative toxicity showed no significant difference between treatment arms of the FLAME trial (11), the large dose range to the bladder and urethra in the FLAME focal boost study allowed for the composition of dose-effect relations for the urethra and bladder, separately. By using a longitudinal repeated measures analysis, we found that an increased dose to the bladder and urethra will result in a significant increase in GU toxicity following EBRT. However, no clear threshold dose for the dose to the urethra and GU toxicity grade ≥2 could be observed. As we found a dose-effect relation for the urethra dose, it would be desirable to optimize the radiation plan also taking the urethra dose into account. We, therefore, propose that focal boost treatment plans should incorporate a urethral dose-constraint (pragmatically set at $D0.1cm^3 \leq 80$ Gy as close to conventional whole prostate gland dose) in addition to the pre-existing bladder dose-constraints. A urethral constraint was incorporated in our subsequent hypo-FLAME study (18). Genitourinary toxicity is multifactorial and depends on other factors than (urethral) dose only. However, when limiting the dose to the bladder and dose to the urethra, we expect to minimize treatment related toxicity.

Whole-gland dose-escalation trials with doses up to 80 Gy, showed higher GU toxicity rates in the dose-escalation arms, showing a dose-effect relation mainly for the high/maximum doses to the bladder and/or urethra (16, 19-22). Frequent GU toxicity complaints are urethral strictures, urinary retention, incontinence and hematuria (13, 19, 23-25). Previous studies showed that an increased dose to the bladder region or urethral surrogate structure receiving >75 Gy (25) and >80 Gy (19), respectively, results in an increase in urethral strictures and urinary obstruction. Mylona et al. also identified the dose to the urethra and bladder sub regions as predictors for various urinary symptoms (24). We found associations for urinary frequency, urinary retention, urinary incontinence and the bladder and urethral dose parameters. A correlation between acute GU toxicity and late GU toxicity was observed. Furthermore, a latency period was present, with GU toxicity occurring years after radiotherapy, including new onset urethral strictures occurring two years, up to seven years, after treatment. This should be taken into consideration and long follow-up is needed to account for (very) late onset genitourinary toxicity.

Strengths of our study are the carefully considered longitudinal analysis that fits our data properly and increases power by using repeated measurements. Another strength is the use of risk groups for presenting the probability of GU toxicity. Notably, these risk groups represent differences in baseline risk of GU toxicity, which is not the same as prognostic modeling and should not be interpreted as such. The unique variation in focal boost dose

used and the lack of a urethral dose-constraint in treatment planning, allowed us to carry out a urethral dose-effect relation analysis for a large dose range. Although the differences in cumulative GU toxicity between the study arms were small and not statistically significant (11), in the present analysis, using the cohort irrespective of randomization, we did observe a dose-effect relation for the bladder and urethra. While this may seem contradictory, this is explained by the observation that in the focal boost arm of the trial, a wide range was found for the dose to the urethra, with some patients receiving a standard dose close to 77 Gy, while others received a much higher dose, depending on the location of the focal boost. The number of patients with a high dose to the urethra in the focal boost arm was too small to observe a significant difference in cumulative GU toxicity. When using cumulative toxicity, the highest toxicity grade at any moment is used to calculate the toxicity rates, not taking into account repeating events of toxicity. Yet, the finding of a significant dose-effect relation for the urethra in the study cohort irrespective of randomization arm, is explained by the longitudinal approach used in the present study. When using repeated measurements, more patients in the focal boost arm had recurring GU toxicity events compared to the standard treatment arm.



Our study has a few limitations. First, the difficulty of delineating the urethra. The urethra was contoured using the T2-weighted sequence of a mpMRI scan (26). Even though the urethra is visualized better on MRI than CT, the delineation of the urethra even on MRI can be difficult and interobserver variation in contouring may exist (27). Second, we used center specific bladder filling protocols. As all participating centers aimed for a comfortably filled bladder, we do not expect this to have influenced our findings. Third, the considerable amount of missing toxicity data is a limiting factor. A generalized linear mixed effect model with random effects to determine the dose-effect relations was used to cope with this limitation. In addition to handling both single and recurring toxicity, these models provide unbiased estimations in the presence of missing data under the missing-at-random assumption (28). Though we have no reason to doubt this assumption, missing-at-random is essentially unverifiable. Fourth, we decided to exclude patients who previously underwent a TURP, as the TURP cavity is not comparable to the anatomical structure of the urethra.
In conclusion, dose-effect relations for both the dose to the bladder and urethra on GU toxicity were observed. For treatment planning of EBRT with a focal boost in the conventional fractionated FLAME scheme, we suggest a dose-constraint for the urethra D0.1cm$^3$ of ≤80 Gy, the optimal urethral dose-constraint for hypofractionated schemes is yet to be determined. Further treatment optimization to increase the focal boost without increasing the dose to the urethra, bladder and other OAR should be a focus for future research, as we have shown that a focal boost improves oncological outcomes in the treatment of prostate cancer.

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# SUPPLEMENTARY MATERIAL

**Table S1.** Stepwise detailed description of statistical analyses:

| **Step 1: Available toxicity data** |
|---|
| Toxicity data was collected by a physician in the four participating centers. The CTCAE 3.0 score was taken weekly during treatment and at one month, six months and yearly thereafter up to ten years. Inherent to a trial with a total follow-up duration of ten years, we had a substantial amount of missing toxicity data. Missing toxicity data percentages per measured time point were comparable between the treatment arms. |
| **Step 2: The implementation of generalized linear mixed effect models** |
| A generalized linear mixed effect model with random effects to determine the urethral and bladder dose-effect relations for GU toxicity grade ≥2 was used. Generalized linear mixed effect models include all available data without excluding subjects with missing follow-up data. With the use of a likelihood-based estimation method, the missing values are estimated based on the existing data (1) under the missing-at-random (MAR) assumption. Although we cannot verify whether the toxicity data was MAR (2,3), we have no reason to doubt this assumption. |
| **Step 3: Fixed and random effects included in model** |
| Fixed effects:<br>*Timediff (dichotomous: acute versus late toxicity)*<br>*Timediff*Time (weeks)*<br>*Institute*<br>*Diabetes mellitus*<br>*Baseline GU toxicity grade ≥1*<br>*Age*<br>*Accumulating dose**<br>*T-stage*<br><br>Random effects: intercept and random slope for Timediff*time, with *Patient ID* as a subject.<br><br>In the analysis, we excluded an overall intercept thereby effectively incorporating a separate intercept for acute and late toxicity. Furthermore, by incorporating the Timediff*time interaction, we allowed for different time effects for acute and late toxicity**. Ideally, random effects should be estimated separately for the intercept and time effects for acute and late toxicity. These models, however, showed numerous convergence problems. We therefore reduced the random effects to include one overall random effect for the intercept.<br><br>**Accumulating dose during treatment = dose-parameter * (time in weeks/7) for the first seven weeks, the full dose was used thereafter*<br>*** An example for this kind of parametrization (albeit a very different application) can be found in the SAS manual: https://documentation.sas.com/doc/en/pgmsascdc/9.4_3.4/statug/statug_glimmix_examples08.htm* |
| **Step 4: Creating dose-effect curves** |
| The estimated probability of GU toxicity grade ≥2 was calculated for the bladder D2cm$^3$ with a dose range of 60-80 Gy in steps of 5 Gy. For the urethral D0.1cm$^3$, the estimated probability of GU toxicity grade ≥2 was calculated with a dose range of 60-100 Gy in steps of 5 Gy.<br><br>To model the dose-effect curve for the average patient we used the prevalence of the risk factors within our cohort. The risk factors were selected based on the available data, literature and physicians experience. A history of diabetes mellitus, a higher T-stage and the presence of baseline GU toxicity grade ≥1 were considered to be risk factors for increased GU toxicity. |

**Table S1**. Continued

| **Step 4: Creating dose-effect curves** |
|---|
| We did not adjust for cardiovascular disease, as it is known that cardiovascular disease and the often prescribed drugs can have a bidirectional effect on toxicity and can be protective or a risk factor for GU toxicity (4-6). Neither did we adjust for hormonal therapy, as (neo)adjuvant hormonal therapy can be protective due to reduction of the prostate volume, but can also be a risk factor for GU toxicity (4). Moreover, we decided to exclude patients who previously underwent a TURP, as we expected that location of the dose to the urethra would be variable and thereby the effect of the dose to GU toxicity would be variable.<br><br>Herold et al. (7) showed that patients with diabetes mellitus have a higher risk of late treatment related GU toxicity. A higher T-stage was considered to be of greater risk for developing GU toxicity, since a higher T-stage could lead to a larger part of the bladder or urethra to be exposed to a higher radiation dose, depending on the location of the tumor. Baseline GU toxicity is known to be a risk factor for radiation induced late GU toxicity and was included in the model.<br><br>Given the dose to the urethra and bladder, respectively, the estimated probability of experiencing GU toxicity grade ≥2 for an average patient having 11% diabetes mellitus, baseline GU toxicity grade ≥1 of 35% and a T-stage with a prevalence of 24% T1c,T2a, T2b combined, T2c 13%, T3a of 42% and T3b, T4 combined of 20% was calculated<br><br>To model the dose-effect curve for a favorable patient, we created a patient with none of the risk factors above present. We calculated the estimated probability of experiencing GU toxicity grade ≥2 for a patient having 0% diabetes mellitus, 0% baseline GU toxicity and the presence of T1c, T2a or T2b.<br><br>To model the dose-effect curve for an unfavorable patient we created a patient with all of the risk factors above present. We calculated the estimated probability of experiencing GU toxicity grade ≥2 for a patient having 100% diabetes mellitus, 100% baseline GU toxicity and the presence of T3b or T4.<br><br>The creation of the (un) favorable dose-effect curves was based on literature and represent the most extreme ranges for GU toxicity possible: a patient with none of the potential risk factors present versus a patient with all potential risk factors present. In reality, all men with prostate cancer who will be treated with external beam radiotherapy according to the FLAME treatment schedule, will have an estimated probability of GU toxicity grade ≥2 that will lie within the range that we provided with our dose-effect curves. |

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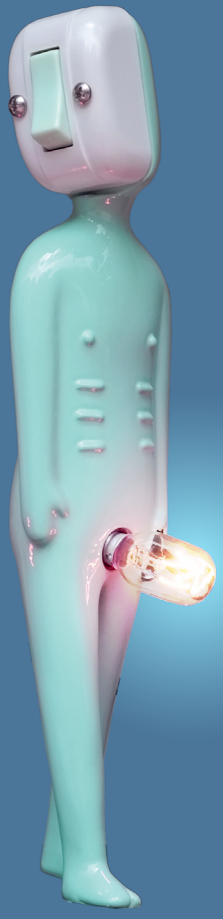


# Patterns of failure following external beam radiotherapy with or without an additional focal boost in the randomized controlled FLAME trial for localized prostate cancer

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## ABSTRACT

**Background**

Focal dose escalation in external beam radiotherapy (EBRT) showed an increase in five-year biochemical disease-free survival in the Focal Lesion Ablative Microboost in prostatE cancer (FLAME) trial.

**Objective**

To analyze the effect of a focal boost to the intraprostatic lesions on local failure-free (LFS) and regional + distant-metastasis-free survival.

**Design, Setting and Participants**

Patients with intermediate- and high-risk localized prostate cancer were included in the phase 3, multicenter, randomized controlled FLAME trial.

**Intervention**

Standard treatment of 77 Gy to the entire prostate in 35 fractions was compared to an additional boost to the macroscopic tumor up to 95 Gy in EBRT.

**Outcome Measurements and Statistical analysis**

LFS and regional + distant-metastasis-free survival, measured by any type of imaging, were compared between the treatment arms using Kaplan-Meier and Cox regression analysis. Dose-response curves were created for local failure (LF) and regional + distant-metastatic failure using logistic regression.

**Results and Limitations**

571 patients were included in the FLAME trial. With a median follow-up of 72 months (interquartile range 58-86), focal boosting decreased LF and regional + distant-metastatic failure with hazard ratios of 0.33 (95% CI 0.14-0.78) and 0.58 (95% CI 0.35-0.93), respectively. Dose-response curves showed that an increased dose to the tumor resulted in reduced LF and regional + distant-metastatic failure rates.

**Conclusion**

A clear dose-response relation for LF and regional + distant-metastatic failure was observed, suggesting that adequate focal dose escalation to the intraprostatic lesions prevents undertreatment of the primary tumor, resulting in an improved regional + distant-metastatic failure.

## PATIENT SUMMARY

Radiotherapy is a treatment option for high-risk prostate cancer. The FLAME trial has shown that a high dose specifically to the tumor within the prostate will result in better disease outcome, with less likelihood of regional and distant disease spread.

## INTRODUCTION

In the Focal Lesion Ablative Microboost in prostatE cancer (FLAME) trial, we showed that focal boosting to the intraprostatic tumor(s) up to 95 Gy in addition to external beam radiotherapy (EBRT) to the whole prostate gland improved biochemical disease-free survival, without significantly increasing toxicity or deteriorating quality of life in patients with intermediate- and high-risk localized prostate cancer (1). The underlying hypothesis was that metastatic failure at the standard radiation dose results partially from undertreatment of the primary tumor.



Since prostate cancer has a long natural disease course, surrogate endpoints for overall survival are often used to measure treatment efficacy (2). (Distant-) metastatic failure occurs more frequently in high-risk patients and the question remains whether micro metastatic spread has already occurred at the time of primary treatment or results from local failure in insufficiently controlled primary tumors (3,4). The primary objective of the present study was to analyze the effect of focal boosting on local failure-free (LFS) and regional + distant-metastasis-free survival. During treatment planning in the FLAME trial, dose-constraints to the organs at risk were prioritized over the focal boost dose to the intraprostatic lesions (5). As a result a large range in focal boost dose was applied, allowing us to perform a dose-response analysis for local failure (LF) and regional + distant-metastatic failure in relation to the focal boost dose.

## MATERIAL AND METHODS

The FLAME trial is a multicenter phase 3 single-blinded randomized controlled trial carried out in the University Medical Center (UMC) Utrecht, The Netherlands Cancer Institute (NKI) in Amsterdam, the Radboudumc in Nijmegen, in the Netherlands and the University Hospitals Leuven (UZL) in Belgium. The research protocol was approved by the medical ethics committee of the UMC Utrecht for the Netherlands (NL26038.041.08) and UZL for Belgium (B322201110225). The FLAME trial was registered at ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT01168479.

Intermediate- and high-risk localized prostate cancer patients, according to the Ash criteria (6), were included between 2009 and 2015. For further analysis the European Association of Urology (EAU) risk classification was used (7). Exclusion criteria were a WHO performance score >2, IPSS score ≥20, evidence of lymph node involvement or distant metastases, a history of pelvic radiation, prostatectomy, trans urethral resection of the prostate (TURP) less than three months prior to radiotherapy and patients who were not able to undergo Magnetic Resonance Imaging (MRI) or had no visible tumor on multiparametric(mp)MRI. All patients gave written informed consent.

Patients were randomized on a 1:1 ratio between treatment arms, with randomization and stratification performed by an independent trial bureau in the UMC Utrecht. Participating center was used as minimization factor to ensure overall balance and balance within each stratum. Participants were blinded for the treatment arm. The investigators could not be blinded, as they were involved in the treatment planning.

(Neo)adjuvant hormonal therapy was prescribed according to clinical practice. Gold fiducial markers were implanted in all patients for position verification during treatment. Patients who were assigned to the standard treatment arm received 77 Gy to the entire prostate in 35 fractions of 2.2 Gy during seven weeks. Patients assigned to the focal boost arm received an additional boost up to 95 Gy to the macroscopic visible tumor. Elective pelvic nodal irradiation was not preformed. Details on the treatment planning have been described previously (1, 8). Target volumes and organs at risk (OAR) were delineated on a planning Computed Tomography (CT) scan and planning mpMRI scan. The intraprostatic lesions, the gross tumor volumes (GTV), were contoured using T2-weighted, Diffusion Weighted Imaging and Dynamic Contrast Enhanced sequences. One or more GTV's could be contoured per patient. The focal boost dose was reduced if needed, to meet the dose-constraints of the OAR.

Biochemical failure was defined as PSA nadir + 2 ng/mL according to the Phoenix criteria (9). As clinical practice changed over time, imaging and treatment after recurrence depended on the time of recurrence and were performed at the discretion of the treating physician. First, we descriptively presented patterns of failure, as detected by any imaging method, at any moment during follow-up. Imaging of clinical failure was divided into local failure defined as recurrent disease confined to the prostate without any metastases, regional failure defined as regional lymph node metastases without local failure and/or distant metastatic failure, and distant metastatic failure defined as distant metastasis without local failure and/or regional failure. The definition of regional lymph nodes was according to the EAU guidelines, including the pelvic lymph nodes below the bifurcation of the common iliac arteries (7). The type of treatment after recurrence, was presented additionally. For survival

analyses we used LF and regional + distant-metastatic failure, defined as the presence of any type of metastases, including regional lymph nodes and distant metastases.
Distant metastasis-free survival, overall- and prostate cancer-specific survival have been reported previously (1). Differences between the treatment arms of the FLAME trial in LFS and regional + distant-metastasis-free survival were assessed with Kaplan-Meier analysis, using log-rank testing. Censoring was applied at date of death or last PSA follow-up date. Additionally, cox regression models were created to adjust for factors potentially associated with clinical failure; Gleason score, T-stage, iPSA, hormonal therapy (duration and timing). Competing risk models were performed according to the Fine and Gray method, with death by any cause as a competing risk.

To investigate the effect of dose on LF and regional + distant-metastatic failure, the association between the near minimum (D98%) dose to the GTV and both failure endpoints were investigated. Dose-response curves were created based on the predicted probabilities of LF and regional + distant-metastatic failure up to seven years, as a function of the near minimum dose to the intraprostatic lesion using logistic regression, based on the entire cohort, irrespective of randomization arm.



All analyses were performed with a per protocol approach using IBM SPSS Statistics 25 and RStudio.

## RESULTS

In the FLAME trial, we included 571 patients with intermediate- and high-risk localized prostate cancer. Median follow-up at the time of the present analysis was 72 months (IQR 58-86 months). Baseline patient characteristics were well balanced between randomization arms and were presented previously (1). The mean age at time of diagnosis was 70 years old (SD 6 years). Using the EAU risk classification, both treatment arms included predominantly high-risk patients (84%). Hormonal therapy was prescribed in 65% of patients in both treatment arms, with the majority receiving adjuvant hormonal therapy. Besides the primary intention-to-treat analysis, we used a per protocol approach, including 271 patients in the standard treatment arm and 264 patients in the focal boost arm. The trial profile, including reasons for exclusion from per protocol analysis, were published previously (1). Imaging in patients with any type of failure at any moment of follow-up (biochemical failure, local failure, regional failure or distant failure) within the per protocol analysis cohort included: bone scintigraphy (n=10/95 (11%), CT scan (12/95, 13%), Positron Emission Tomography (PET)/CT (n=77/95, 81%); of which Choline (n=12/95, 13%) and PSMA (n=68/95, 72%) and mpMRI (n=25/95, 26%).

The prevalence of clinical failure per anatomical site per treatment arm was presented in Table 1. Treatment for recurrent prostate cancer was administered in 40 patients in the standard treatment arm and 26 patients in the focal boost arm. Systemic therapy, consisting of hormonal treatment was the most common treatment type. Kaplan-Meier curves showed a significant difference between the treatment arms for LFS (Log-rank p=0.008) and regional + distant-metastasis-free survival (Log-rank p=0.02) (Figure 1).

**Table 1.** Prevalence of total clinical failure per anatomical site

| | | Randomization | |
|---|---|---|---|
| | | **Standard arm, (total=271)** | **Focal boost arm, (total=264)** |
| | | **N** | **N** |
| | Local Failure | 21 | 7 |
| | Regional Failure | 22 | 7 |
| Distant Failure | Distant Lymph Node | 13 | 11 |
| | Bone | 15 | 12 |
| | Visceral | 6 | 2 |
| Treatment after recurrence | Systemic therapy | 24 | 15 |
| | Local therapy prostate | 5 | 4 |
| | Metastasis-directed therapy (oligometastases) | 9 | 5 |
| | Palliative radiotherapy | 1 | 1 |
| | Other | 1 | 1 |

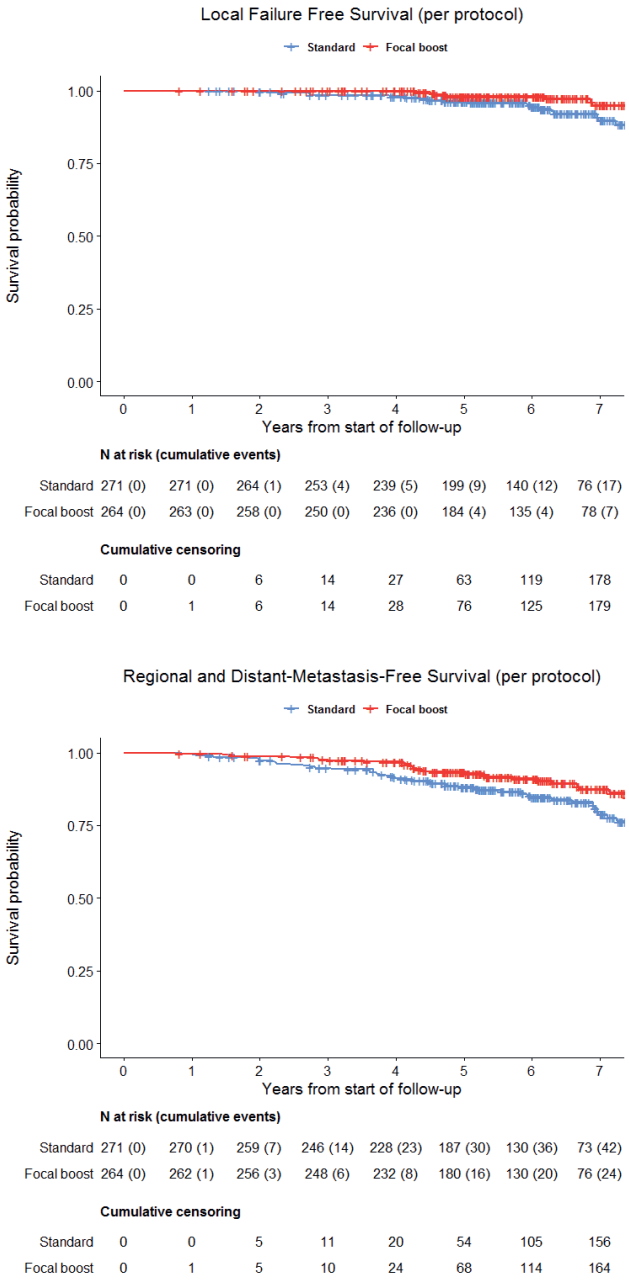


**Figure 1.** Kaplan-Meier curves for Local Failure Free Survival (p<0.01) and Regional + Distant Metastasis-Free Survival (p=0.02) comparing the standard treatment of 77 Gy in 35 fractions to the whole prostate with an additional focal boost to the macroscopic visible tumor up to 95 Gy

In cox regression analysis, we observed differences in favor of the focal boost arm for both LF and regional + distant-metastatic failure with adjusted hazard ratios of 0.33 (95% CI 0.14-0.80, p=0.01) and 0.56 (95% CI 0.34-0.91, p=0.02), respectively (Table 2). When performing a competing risk analysis according to the Fine and Gray methods, similar results were found, with a hazard ratio of 0.32 (p=0.01) for LF and a hazard ratio of 0.56 (p=0.02) for regional + distant-metastatic failure. Dose-response curves showed a decreased predicted probability for LF and regional + distant-metastatic failure up to seven years when increasing the dose to the GTV. With a focal boost dose of ≥ 85 Gy, the predicted probability of LF approached zero (Figure 2A), for regional + distant-metastatic failure a predicted probability of less than 10% was observed at a focal boost dose of ≥ 85 Gy (Figure 2B) compared to 15% at the standard dose of 77 Gy.

**Table 2** –Results of Cox Regression Analysis for Local Failure and Regional + Distant-Metastatic Failure, adjusted for Center, Age (years), Hormonal Treatment Duration (months), Timing of Hormonal Treatment (Neoadjuvant versus Adjuvant), T-Stage, Initial PSA (ng/mL), and Gleason Score.

| Cox regression (per protocol) | | |
|---|---|---|
| | **Adjusted HR*** | **95% CI, p-value** |
| Local Failure | 0.33 | 0.14-0.80, p=0.01 |
| Regional + Distant-Metastatic Failure | 0.56 | 0.34-0.91, p=0.02 |

## DISCUSSION

In this secondary analysis of the FLAME trial, we demonstrated that focal boosting up to 95 Gy significantly improved LFS and regional + distant-metastasis-free survival. The regional + distant-metastatic failure was reduced nearly by half in the focal boost arm, compared to standard treatment. Moreover, the dose-response curves indicated that a higher dose on the primary tumor will result in reduced LF and regional + distant-metastatic failure. Since we observed a significantly higher regional + distant-metastatic failure in the standard treatment arm compared to the focal boost arm, our findings support the hypothesis that undertreatment of the primary tumor is one of the factors contributing to the development of regional + distant-metastatic failure. This is remarkable, as the FLAME trial only involved local irradiation of the prostate with a geometrical margin around the prostate for uncertainties.

Despite the reduced regional + distant-metastatic failure that resulted from an improved local control by focal boosting, the dose-effect relation indicates that regional + distant-

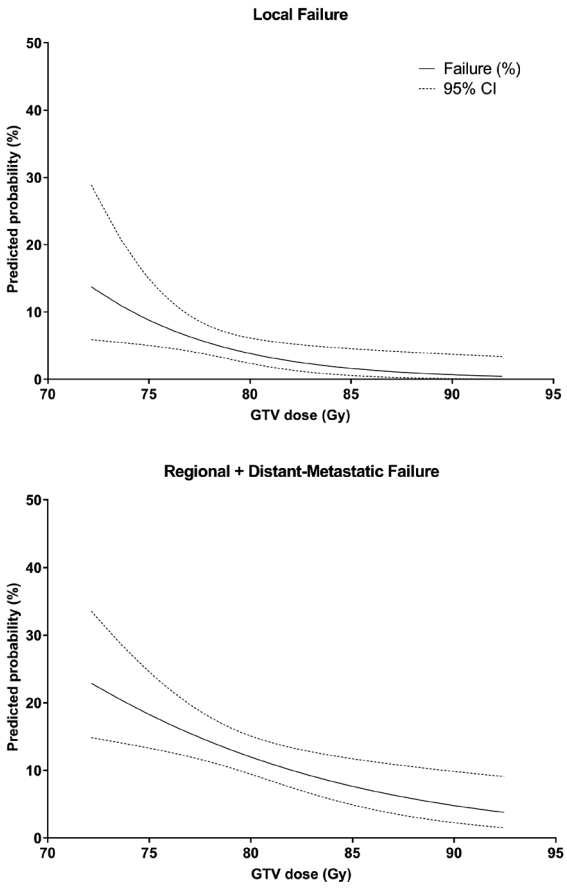


**Figure 2.** Predicted probability of A. Local Failure and B. Regional + Distant-Metastatic Failure up to 7 years as a function of achieved dose to the gross tumor volume (GTV) (D98%; Gy)

metastatic failure still may occur even at a high focal boost dose. This might be attributable to the presence of micro metastasis at the time of diagnosis. At a median follow-up of 72 months, we previously observed similar overall- and prostate cancer-specific survival rates in the treatment arms of the FLAME trial. It should be noted that the study was not powered for survival endpoints and the follow-up time is relatively short for these endpoints (1). Other whole-gland dose-escalation trials showed increased biochemical disease-free survival when escalation the dose to the prostate (11-14). Definitions for secondary endpoints differed per trial. In the MD Anderson trial, distant-metastatic failure was significantly lower in the dose-escalation arm, which translated into improved prostate cancer-specific mortality in the dose-escalation arm (11). The MRC RT01 trial did not find

a difference in metastasis-free survival (12). Heemsbergen et al. did not present (distant-) metastasis-free survival. They did not observe a difference in clinical failure-free, overall- and prostate cancer-specific survival at 110 months follow-up (13). The GETUG 06 trial did not assess (distant-)metastasis-free survival either, and they did not find a difference in overall survival at five years follow-up (14).

In the ASCENDE-RT trial, an improved biochemical disease-free survival was observed by using a whole gland brachytherapy boost after EBRT, comparable to the benefit in biochemical disease-free survival for the FLAME focal boost arm. At a median follow-up of 6.5 years, they did not observe differences in metastasis-free survival. Additionally, no differences in overall- and prostate cancer-specific survival were observed for the brachytherapy boost arm (15).

Long follow-up is needed in clinical trials for prostate cancer and an inevitable limitation is the clinical practice changing over time. In the present study, imaging for biochemical recurrence was used without routine histopathological confirmation to assess local failure and (distant-)metastatic failure as per standard clinical practice. At the start of the FLAME trial, guidelines on imaging and treatment for biochemical failure did not exist. Nevertheless, in most patients with biochemical failure, PET-imaging was acquired, resulting in reliable disease staging. The recently published meta-analysis of Gharzai et al. validated metastasis-free survival as a surrogate endpoint for overall survival (2). However, it is unclear if regional + distant-metastasis-free survival has a similar surrogacy for overall survival. In current practice, imaging is performed at an earlier stage with improved imaging techniques including PSMA-PET scans which may lead to stage migration. Earlier detection of regional and distant failure with fewer and smaller lymph node and bone metastases is likely to occur, potentially leading to a weaker correlation with overall survival (2). Notably, the difference in regional + distant-metastasis-free survival is likely to be driven by regional recurrence instead of distant metastasis.

Another limitation is the heterogeneity in definitions used for metastatic failure, making it difficult to compare the oncological outcomes of clinical trials. With definitions for metastatic failure varying from distant metastases with or without regional lymph node metastases, and with or without death by any cause. Notably, in the meta-analysis of Gharzai et al., the strong correlation between metastasis-free survival and overall survival might partially be driven by the inclusion of death by any cause as an event in metastasis-free survival. In the multivariable models of the present study, tumor size was not taken into consideration, which could be a limitation as Woo et al. showed in a meta-analysis that a larger tumor size is a risk factor for biochemical and metastatic failure (16). In radiotherapy

trials that allow hormonal therapy, the question arises what role the (neo)adjuvant hormonal therapy played on the oncological outcomes. Although we adjusted for duration of hormonal therapy and neo-adjuvant or adjuvant hormonal therapy in the multivariable models, stratification for hormonal therapy in the dose-response modelling was considered inappropriate since the study was not powered for this comparison and potential effect modification by hormonal therapy is also dependent on the duration and its timing.

A strength of our study was the range in the focal boost dose to the intraprostatic lesions that allowed us to create dose-response curves for LF and regional + distant-metastatic failure. These dose-response curves strengthen our findings in the patterns of failure analysis and, thereby, support the hypothesis that regional + distant-metastatic failure at least partially results from undertreatment of the primary tumor. The large number of patients included in the FLAME trial, the collaboration of multiple participating centers and the use of modern-day radiotherapy techniques without the need for additional technology or equipment, increase generalizability of the FLAME trial and allow for implementation of the FLAME schedule without additional costs.



Since we have shown that focal boosting improves not only biochemical disease-free survival but also regional + distant-metastasis-free survival, increasing precision in treatment planning becomes even more important. Van Schie et al. published that by replanning, the focal boost dose can be increased on conventional linear accelerators (5). Furthermore, the use of MR-guided radiotherapy will allow for improved targeting accuracy and a higher focal boost dose by daily online plan adaptation without violating the dose-constraints to the OAR (17).

Extreme hypofractionation has shown to be non-inferior to conventional fractionation in terms of biochemical disease-free survival and overall survival, with benefits in patient convenience and a reduced workload for radiotherapy departments (18, 19). The combination of extreme hypofractionation and focal boosting according to the FLAME trial technique was tested in the prospective multicenter phase 2 Hypo-FLAME trial and was considered safe regarding acute toxicity (20). Long term results on biochemical disease-free survival and other survival endpoints are to be investigated.

In conclusion, focal boosting up to 95 Gy in the FLAME trial improved LF and regional + distant-metastatic failure in patients with localized mainly high-risk prostate cancer. The dose-response analyses showed the benefit of higher doses to the tumor on LF and regional + distant-metastatic failure. Therefore, focal boosting might be beneficial even when a dose of 95 Gy cannot be reached due to the dose-constraints to the OAR. Our findings support

the hypothesis that undertreatment of the primary tumor is likely to contribute to the development of regional + distant-metastatic failure. Focal boosting should be considered standard of care in EBRT for high-risk prostate cancer treatment.

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CHAPTER 6

# General discussion

## THE CONCEPT OF FOCAL BOOSTING

Whole gland dose escalation in external beam radiotherapy (EBRT) for prostate cancer effectively increases biochemical disease-free survival, at the cost of increasing toxicity (1–4). In 2018, based on a large meta-analysis, Vogelius and Bentzen suggested that dose escalation with conventional or hypofractionation schedules, had reached a ceiling at an EQD2 of 80 Gy (5). This 'ceiling' was hypothesized to be explained by either a maximum biochemical disease-free survival that can be reached with any type of local therapy for prostate cancer or the fractionation sensitivity of prostate cancer decreases with increasing fraction size (5,6). An alternative technique for dose escalation, potentially without increasing toxicity, is focal boosting. Single arm feasibility studies showed that (focal) boosting is feasible and could lead to improved oncological outcomes (7). The hypothesis that focal boosting increases biochemical disease-free survival by improved local control in intermediate and high-risk prostate cancer was tested in the FLAME trial (NCT01168479). The FLAME trial is the first phase 3 randomized controlled trial that showed improved biochemical disease-free survival by applying a focal boost in addition to whole-gland EBRT (chapter 2). To use the words of Vogelius and Bentzen, the FLAME focal boost thereby appears to have "cracked the ceiling" (8) and proved the concept of focal boosting. By cracking the suggested ceiling, with an increase in biochemical disease-free survival up to 92% in the focal boost arm, the hypothesis that fractionation sensitivity of prostate cancer decreases with increased fraction size, became more likely. Since focal boosting in the FLAME trial reduced biochemical recurrences and local recurrences by half (chapter 2 and 5), it is essential to further investigate the potential of focal boosting, especially when combined with ultra-hypofractionation.

## THE IMPACT OF FOCAL BOOSTING ON TOXICITY AND QUALITY OF LIFE

Treatment-related toxicity is the main challenge in dose escalation and (focal) boosting delivered for prostate cancer. In the FLAME trial, the 'iso-toxic focal boost' concept was successful and no statistically significant difference in toxicity rates occurred when adding a focal boost. Toxicity rates in the FLAME trial were comparable to whole-gland dose escalation trials (9,10). When compared to whole gland boost trials, for example the ASCENDE-RT trial, late grade 3 genitourinary toxicity in the focal boost arm of the FLAME trial was lower (9% vs 6%, respectively) (11). Radiation induced toxicity is dependent on multiple factors, and the strongest predictors are yet to be determined. Firstly, toxicity is influenced by technical and treatment-related factors; 1) all influencing delivered dose to

the organs at risk, such as the dose to clinical and planning target volumes and subsequent margins used, and the dose to the organs at risk, 2) the radiotherapy schedule, i.e. conventional fractionated versus moderate to ultra-hypofractionated radiotherapy, 3) the time between fractions, 4) overall treatment time, 5) the type of accelerator used, i.e., the Cyberknife (12), a standard linear accelerator or a linear accelerator combined with MRI (13), 6) the use of gold fiducial markers and 7) the administration of (neo)adjuvant hormonal therapy (14–17). Secondly, patient characteristics might influence toxicity including anatomy (i.e., prostate volume or prostate protrusion), higher T-stage (T3a, T3b or T4), a patient history of pelvic surgery, TURP or prior radiotherapy, pre-treatment lower urinary tract symptoms with a high IPSS score (18), chronic diseases, i.e., inflammatory bowel disease and certain drug use (14–17,19). Thirdly, treatment related toxicity in literature is reported with different types of scoring systems, i.e., RTOG (20) and CTCAE (21), making results more difficult to compare.

Overall, late grade ≥2 genitourinary toxicity was observed more frequently than late grade ≥2 gastrointestinal toxicity in radiotherapy trials addressing dose escalation and (focal) boosting, (2,11,22,23). The outcomes of dose-effect modelling for genitourinary and gastrointestinal toxicity in the FLAME trial showed, as expected, that an increased dose to the organs at risk will lead to significantly higher grade ≥2 toxicity rates, regardless of the treatment arm (**chapter 3 and 4**). These models confirm the importance of strict adherence to the dose-constraints of the organs at risk and keeping the dose to the organs at risk as low as possible.



A dose-constraint for the urethra should be considered in treatment planning for a focal boost radiotherapy schedule. Urethra sparing has previously been described in studies on ultra-hypofractionated radiotherapy. Studies that used a urethral constraint appeared to have lower genitourinary toxicity rates compared to non-urethra sparing ultra-hypofractionation schedules (24,25). The delineation of the urethra comes with challenges. The use of multiparametric MRI is essential for the delineation of the urethra, and even so, it can be difficult to delineate. Solutions that have been suggested to aid in urethral delineation are the use of an indwelling urinary catheter or real time MRI micturating urethrography during imaging for treatment planning and sometimes during radiation treatment (26,27).

Although gastrointestinal toxicity rates are low, it is worthwhile to prevent any potential radiation induced toxicity. If a dominant intraprostatic lesion lies approximate to the rectum, the focal boost dose should be compromised to not exceed the rectal dose constraint. Rectal spacers and endorectal balloons have been successfully tested to reduce treatment-

related gastrointestinal toxicity (28). Although gastrointestinal toxicity occurs less frequent than genitourinary toxicity, in the specific situation that a focal boost dose is difficult to reach, or if a patient is at risk of increased gastrointestinal toxicity due to for instance inflammatory bowel disease, a rectal spacer or endorectal balloon may be considered.

As prostate cancer has a long natural disease course and life expectancy has increased with improved treatment options, treatment-related toxicity and quality of life are important secondary endpoints to take into consideration in clinical trials. In the FLAME trial, quality of life did not deteriorate by adding the focal boost (**chapter 2**).

## PATTERNS OF FAILURE FOLLOWING FOCAL BOOSTING

In the FLAME trial, it was hypothesized that metastatic failure following radiotherapy for prostate cancer is partially attributed to undertreatment of the primary tumor. Patterns of failure analyses showed that the addition of a focal boost reduced local failure by more than half and showed a decrease in regional- plus distant metastatic failure (**chapter 5**). However, isolated distant metastatic failure, which was identified as a surrogate endpoint for overall survival in prostate cancer in the meta-analysis of Gharzai et al.(29), was not reduced by the addition of a focal boost to EBRT. The dose-response curve for distant metastatic failure (**chapter 2**), local failure and regional and distant failure combined showed a decrease in failure with an increase in the median focal boost dose (**chapter 5).** We did not observe differences in prostate cancer-specific survival and overall survival (**chapter 2**). Notably, not all patients in the focal boost arm received a focal boost up to 95Gy due to dose constraints to the organs at risk. Optimization of future treatment plans could result in higher focal boost doses and, subsequently, improved oncological outcomes. Furthermore, 72 months is a relative short follow-up period to determine survival endpoints for the long natural disease course that is associated with prostate cancer, and the FLAME trial was not powered to test these survival endpoints. The use of surrogate endpoints for overall or prostate cancer-specific survival is useful in clinical trials, due to the long natural disease course in prostate cancer. Surrogate endpoints for overall and disease-specific survival arise from previous trial results. These results are inevitably subjected to diagnostic and therapeutic changes in the management of prostate cancer over time. The surrogate endpoints that are now being used, are determined based on recurrence patterns in the time of conventional imaging with lower detection rates of metastatic disease, often performed at a later time during follow-up, with a more progressed disease stage (30). Moreover, metastasis directed therapy is performed more often and led to earlier treatment of oligo-metastases. In some trials, metastasis directed therapy has increased the time to subsequent systemic therapy and

improved biochemical failure-free survival and overall survival (31). Hence, distant metastatic failure as surrogate endpoint might not be as predictive for overall or disease-specific survival, as the results of a meta-analysis suggest (29,32).

There is an ongoing debate whether elective irradiation of the pelvic lymph nodes is beneficial in terms of oncological outcomes in high-risk prostate cancer patients. It is argued that prostate-only radiotherapy does not cover all (micro-metastasized) lesions in the pelvic area. Elective nodal radiotherapy was not performed in the FLAME trial. The POP-RT trial compared whole pelvis radiotherapy to prostate-only radiotherapy in high-risk nodal negative patients (80% was staged by PSMA-PET imaging) (34) and observed a biochemical disease-free survival of 95% in the nodal pelvic radiotherapy arm versus 81% in the prostate only radiotherapy arm. Cumulative late grade ≥ 2 GU toxicity was significantly higher in the pelvic radiotherapy arm (20% versus 9%, P=0.02). Notably, pelvic irradiation also leads to other tissue related toxicity that may not clearly be identified when scoring toxicity and QoL, i.e., radiotherapy induced fibrosis, making future abdominal surgery more complicated (35). If optimizing local control by administering a focal boost can result in lower regional failure, as was suggested by the FLAME trial results, elective nodal radiotherapy might be omitted. Notably, the POP-RT trial and the FLAME trial are not directly comparable as it involves a different patient selection, with the possibility that the POP-RT trial included higher risk patients.



The STAMPEDE trial is a multi-arm, multistage platform protocol with several ongoing phase 3 randomized controlled trials. One of the randomized controlled trials of STAMPEDE is investigating the addition of abiraterone acetate with prednisolone to local radiotherapy combined with hormonal therapy in patients with high-risk non-metastatic prostate cancer (36). In a meta-analysis of two STAMPEDE trials, the combination-therapy group (radiotherapy, hormonal therapy, and abiraterone) showed a 6-year survival rate 82% (95% CI 79-85), while the control group (radiotherapy and hormonal therapy) had a lower rate of 69% (95% CI 66-72). The hazard ratio for the combination-therapy group compared to the control group was of 0.53 (95% CI 0·44-0·64, p<0·0001), indicating a significant difference. It should be noted that STAMPEDE enrolled extremely high-risk prostate cancer patients, including 39% node-positive patients on CT-scan. In the first two years, the combination-therapy group showed an increased risk of late grade ≥3 adverse events of eight percent in the abiraterone group compared to the control group (36). For the high-risk node negative patients, it might not be necessary to add abiraterone to every treatment regimen at the cost of increased severe toxicity since the FLAME trial already showed excellent oncological outcomes. While the FLAME trial, POP-RT trial, and STAMPEDE trial each included high-risk patients, it is possible that the patients in the FLAME trial might be of somewhat lower risk compared to those in the other trials

# THE COMBINATION OF HYPOFRACTIONATION AND FOCAL BOOSTING

**Moderate hypofractionation**

Moderate hypofractionation schedules were introduced with the aim to improve oncological outcomes and reduce treatment-related toxicity by using fewer fractions with higher doses. The CHHiP trial (37) and HYPRO trial (38) both tested moderate hypofractionation and showed non-inferiority when compared to conventional fractionation schedules. Now that the concept of focal boosting is proven, it is interesting to go further and investigate the addition of a focal boost to hypofractionation. The combination of a focal boost and moderate hypofractionation is being tested in the DELINEATE trial (39). Standard conventional radiotherapy (74 Gy in 37 fractions) with an integrated boost up to 82 Gy was compared to moderately hypofractionated radiotherapy (60 Gy in 20 fractions) with an integrated boost up to 67 Gy (39). The first results of an interim analysis showed acceptable grade ≥2 gastrointestinal and genitourinary toxicity (RTOG) in both treatment groups, with higher toxicity rates in the moderate hypofractionation group. At one year follow-up, the standard fractionation group showed 4% grade ≥2 gastrointestinal toxicity and almost no grade ≥2 genitourinary toxicity, versus 8% and 10%, respectively, in the moderate hypofractionation group (40). At five years follow-up, grade ≥2 gastrointestinal toxicity was 13% in the standard treatment cohort and 21% in the moderate fractionation cohort. For genitourinary toxicity this was 13% versus 18%, respectively. Oncological outcomes showed a five-year freedom from biochemical/clinical recurrence of 98% versus 95%, respectively (41).

**Ultra-hypofractionation**

Ongoing non-inferiority trials are comparing conventionally fractionated and moderate hypofractionation of twenty or more fractions with ultra-hypofractionation, using five to seven fractions (42,43). Ultra-hypofractionation showed non-inferiority compared to conventionally fractionated radiotherapy in the HYPO-RT-PC trial (43). The PACE-B randomized controlled trial combined moderate hypofractionation (62Gy in 20 fractions) and conventional fractionation (78 Gy in 39 fractions) as one group and compared these modalities with ultra-hypofractionation (36.25Gy in 5 fractions with a concomitant boost to the CTV up to 40 Gy) in men with low and low-intermediate risk prostate cancer. Hormonal therapy was not permitted. Toxicity was assessed every three months up to two years, using both the RTOG and CTCAE toxicity scales. Two-year toxicity results of the PACE-B trial were promising with similar RTOG toxicity rates in both treatment arms, oncological outcomes are to be published (17).

The combination of focal boosting and ultra-hypofractionation (five fractions) is being tested in multiple phase 2 trials (i.e., hypo-FLAME (44), hypo-FLAME 2.0 (NCT04045717), DELINEATE-HYPO (40), SPARC (45), 5STAR (46)). The first results of these studies on feasibility and safety are promising (44–46). Whether this combination yields long-term oncological outcomes similar to the FLAME trial is yet to be determined. Therefore, focal boosting combined with ultra-hypofractionation should be compared to conventionally fractionated and moderate hypofractionated treatment schedules, which is performed in the hypo-FLAME 3.0 (NCT05705921) and the HypoFocal-SBRT trial (47). With the introduction of MRI-guided radiotherapy, hypofractionation trials became more extreme, by reducing the number of fractions even further. The phase 2 2STAR trial and 2SMART trial tested radiotherapy schedules of two fractions without a focal boost in low- and intermediate-risk prostate cancer patients and showed feasibility with acceptable toxicity (48). Long-term oncological and toxicity outcomes are to be awaited. The HERMES trial is now recruiting patients and is investigating 36.25 Gy in five fractions including a focal boost dose up to 40 Gy compared to 24 Gy in two fractions with a focal boost dose up to 27 Gy with MRI-guided radiotherapy (NCT04595019). Ultra-hypofractionation schedules are beneficial in terms of patient convenience due to fewer hospital visits and are also likely to improve cost-effectiveness which is favorable for radiation oncology departments and health care costs in general (49). The ultimate radiotherapy schedule is yet to be determined.



## ALTERNATIVE WAYS TO BOOST

**LDR brachytherapy**

The general concept of boosting in radiotherapy was strengthened by the outcomes of the ASCENDE-RT trial that applied a whole-gland LDR brachytherapy boost and improved five-year biochemical disease-free survival up to 89% compared to 84% in the standard treatment arm (33).

In this phase 3 randomized controlled trial, all patients received 46 Gy (23 fractions) to the whole pelvis and were prescribed neo-adjuvant hormonal therapy. Additionally, a whole-gland LDR brachytherapy boost (115 Gy) was compared to additional conventional fractionation of 32 Gy (16 fractions), adding up to 78 Gy in total (39 fractions) (11).

**HDR brachytherapy**

Another form of radiotherapy is High Dose Rate (HDR) brachytherapy, using a temporary radioactive source to deliver brachytherapy into the prostate. HDR brachytherapy is often used in the recurrent setting of prostate cancer (50). In the TARGET phase 2 trial (51) and

in the PIVOTALboost phase 3 randomized controlled trial (52), HDR brachytherapy is used to deliver a MR-guided focal boost to the dominant intraprostatic lesion in the primary setting. In the TARGET trial, the HDR focal boost arm achieved a higher mean and maximal focal boost dose compared to the integrated focal boost dose in the EBRT arm, with comparable quality of life and acute physician reported toxicity outcomes (51). In the PIVOTALboost trial, moderate hypofractionation EBRT with or without pelvic nodal irradiation is compared to moderate hypofractionation EBRT combined with a focal boost administered with EBRT or HDR brachytherapy, with or without pelvic irradiation (52). The oncological outcomes of the PIVOTALboost and TARGET trial are to be awaited.

The TROG 03.04 RADAR phase 3 randomized trial compared the administration of six months hormonal therapy with 18 months of hormonal therapy in patients who received different conventional fractionation EBRT schedules (66-74 Gy), or 46 Gy EBRT combined with an HDR brachytherapy boost. This study found that a longer duration of hormonal therapy reduced distant disease progression, regardless of the radiotherapy schedule. Furthermore, they observed that distant disease progression was significantly lower in the HDR brachytherapy boost group compared to EBRT with 70 Gy EBRT, irrespective of hormonal therapy duration (53). It should be noted that the RADAR trial did not randomize based on radiotherapy treatment modalities and results should be interpreted with caution. Moreover, in the RADAR trial relatively low treatment schedules were chosen, with 70Gy not being representative of the higher dose schedules that were used at the time. Although the combination of EBRT with an HDR brachytherapy boost and hormonal therapy of at least 18 months showed promising results, randomized controlled trials should be performed to confirm the superiority of the boost method that is being used.

## THE ROLE OF MR-GUIDED RADIOTHERAPY IN FOCAL BOOSTING

Magnetic Resonance Image-guided radiotherapy (MRIgRT), is the combination of MR imaging with a linear accelerator and allows for online adaptation based on the daily anatomy during radiotherapy. With MRIgRT, high precision radiotherapy with further margin reduction and online adaption became possible (54). The MIRAGE randomized controlled trial compared MR-guided SBRT with CT-guided SBRT and showed a 60% reduction in odds of acute grade two genitourinary toxicity. This reduction in toxicity was accomplished with MRIgRT due to margin reduction of the prostate and seminal vesicles (55). An early cost-effectiveness study by Hehakaya et al. (56), showed that implementation of the MR-Linac in radiotherapy for prostate cancer in five fractions is cost-effective when compared to

EBRT of 20 or more fractions. When compared to ultra-hypofractionation of five fractions SBRT, the implementation of the MR-Linac appeared cost-effective at a toxicity reduction of 54% (56). The reduction of acute genitourinary toxicity in the previously mentioned MIRAGE study (55) is promising. It is likely that the MR-Linac can be cost-effective in radiotherapy for prostate cancer. The combination of focal boosting and ultra-hypofractionation using MRIgRT in locally advanced prostate cancer patients will be evaluated in the AFFIRM trial (NCT05373316). Future research will provide us more insights on efficacy and cost-effectiveness of combined focal boosting and ultra-hypofractionation with even fewer treatment fractions, using MRIgRT.

## CLOSING REMARKS

Overall, the concept of focal boosting has been proven to be beneficial in terms of biochemical disease-free survival with no extra costs or patient visits and can be performed on a conventional Linac. Furthermore, it is non-invasive when compared to an LDR or HDR brachytherapy boost. Even though a difference in survival endpoints was not observed in the FLAME trial, the benefit in decreased local failure and regional- and distant metastatic-failure combined, is still very relevant for patients. Lower failure rates will lead to lower health costs and improved quality of life, as patients do not have to live with the burden of having recurrent disease and its secondary treatment.



The ongoing hypofractionation trials will teach us more on the combination of focal boosting and ultra-hypofractionation. Whether these two strategies combined will go beyond the biochemical disease-free survival of 92% observed in the FLAME trial, is yet to be determined. These trials will also shine light upon the question whether there is a limit to the relative biological effect as suggested in the dose-response relationship of the meta-analysis by Vogelius and Bentzen (8,57).

This thesis evaluates the benefit of an additional focal boost to EBRT in intermediate- and high-risk prostate cancer patients. While doing so, the results of the FLAME trial are practice changing and the FLAME focal boost schedule should be implemented as standard treatment in conventionally fractionated EBRT regimens in patients with high-risk prostate cancer. It is time to light the FLAME.

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# APPENDICES

English summary

Nederlandse samenvatting (Dutch summary)

Scientific publications and presentations

Dankwoord

Curriculum Vitae

# ENGLISH SUMMARY

Prostate cancer is the most frequent diagnosed type of cancer in middle-aged men. Treatment options for localized prostate cancer include active surveillance, watchful waiting, and local therapy such as surgical removal of the prostate (prostatectomy) or radiotherapy (external beam or brachytherapy), with or without hormonal therapy and/or pelvic lymph node dissection. Multiparametric Magnetic Resonance Imaging (mpMRI) is playing an increasingly significant role in the diagnosis of prostate cancer, as well as in radiotherapy for the prostate. Increasing the radiation dose to the entire prostate leads to improved biochemical recurrence-free survival. However, this also increases the risk of side effects due to a higher radiation dose to surrounding organs. Local recurrences after external beam radiotherapy of the prostate are often found at the location of the primary tumor, suggesting that the dose to the primary tumor was not high enough. These local recurrences can eventually lead to distant metastases, resulting in an increased risk of prostate cancer-related death. A higher dose specifically to the visible tumor in the prostate, could potentially improve local tumor control (and subsequently metastasis-free survival), without increasing the risk of toxicity or deteriorating quality of life.

In 2009, the multicenter phase III randomized Focal Lesion Ablative Microboost in prostatE cancer (FLAME) trial was initiated, which compared a conventional radiation schedule of 77 Gy in 35 fractions to the entire prostate with or without a focal boost to the visible tumor up to 95 Gy in patients with intermediate- and high-risk localized prostate cancer. The primary endpoint of the FLAME trial was five-year biochemical recurrence-free survival. Secondary endpoints were treatment-related toxicity scored by the treating physician, and quality of life scored by the patient. The five-year biochemical recurrence-free survival in the focal boost arm was 92%, which was significantly better compared to 85% in the standard arm. The FLAME trial has thereby demonstrated that the concept of a focal boost is effective (**Chapter 2**). The focal boost in the FLAME trial did not result in a significant increase in toxicity and did not affect the quality of life. The development of radiation-related toxicity is dependent on many factors. Dose-response relationships for gastrointestinal (**Chapter 3**) and genitourinary (**Chapter 4**) toxicity show that an increase in dose to the surrounding organs will lead to an increase in toxicity. The dose to the urethra, in particular, has a strong influence on genitourinary toxicity. It is therefore important to consider the urethra as a risk organ when planning a radiotherapy schedule, and to avoid high doses to the urethra. The introduction of MRI in radiotherapy planning makes it possible to delineate the urethra. In the FLAME trial, more genitourinary toxicity was observed than gastrointestinal toxicity (**Chapter 2**). Analysis of the number of local recurrences, regional, and distant metastases, shows that adding a focal boost reduces the number of local recurrences by

half and also decreases the combined number of regional and distant metastases (**Chapter 5**). No difference was found in distant metastases, overall survival, or prostate cancer-specific survival between the two study arms. While there was no difference in distant metastases between the two study arms, a dose-response relationship was observed between the focal boost dose and the risk of distant metastases. A longer follow-up period will determine whether this has an impact on the risk of distant metastases and prostate cancer-specific survival in the focal boost arm.

# NEDERLANDSE SAMENVATTING

Prostaatkanker is de meest voorkomende kankersoort gediagnostiseerd bij mannen vanaf middelbare leeftijd. Behandelopties voor het gelokaliseerd prostaatcarcinoom bestaan uit actief volgen, waakzaam afwachten en lokale therapie in de vorm van het operatief verwijderen van de prostaat (prostatectomie) of bestraling van de prostaat (uitwendige radiotherapie of brachytherapie), al dan niet gecombineerd met hormonale therapie en/of pelviene lymfeklierdissectie. Multiparametrische Magnetic Resonance Imaging (mpMRI) speelt een steeds grotere rol in de diagnostiek van prostaatkanker, maar ook voor radiotherapie van de prostaat. Verhoging van de radiotherapie dosis op de gehele prostaat geeft verbeterde de biochemisch recidief vrije overleving. Echter, dosisverhoging op de gehele prostaat geeft een verhoogde kans op bijwerkingen door een hogere dosis op omliggende organen. Lokale recidieven na uitwendige bestraling van de prostaat worden vaak gevonden op de locatie van de primaire tumor, hetgeen suggereert dat de dosis op de primaire tumor niet hoog genoeg was. Deze lokale recidieven kunnen uiteindelijk resulteren in afstandsmetastasen met als gevolg een verhoogde kans op prostaatkanker gerelateerd overlijden. Een hogere dosis specifiek op de zichtbare tumor in de prostaat, zou de lokale tumor controle (en daarmee metastasevrije overleving) mogelijk kunnen verbeteren, zonder hogere kans op toxiciteit of vermindering van de kwaliteit van leven.

In 2009 is de multicenter fase drie gerandomiseerde Focal Lesion Ablative Microboost in prostatE cancer (FLAME) trial gestart, waarbij een conventioneel bestralingsschema van 77 Gy in 35 fracties op de gehele prostaat in patiënten met of zonder focale boost op de zichtbare tumor tot 95Gy werd vergeleken bij patiënten met matig- en hoog-risico gelokaliseerde prostaatkanker. Het primaire eindpunt van de FLAME trial was vijf-jaars biochemisch recidief-vrije overleving. Secundaire eindpunten waren bestralings-gerelateerde toxiciteit, gescoord door de behandelend arts en kwaliteit van leven, gescoord door de patiënt. De vijf-jaars biochemisch recidief-vrije overleving in de focale boost arm was 92% en daarmee significant beter vergeleken met 85% in de standaard arm. De FLAME trial heeft daarmee aangetoond dat het concept van een focale boost werkt (**hoofdstuk 2**). De focale boost in de FLAME trial gaf geen significante toename van toxiciteit en beïnvloedde de kwaliteit van leven niet. Het ontstaan van bestralings-gerelateerde toxiciteit is afhankelijk van veel factoren. Dosis-effect relaties voor gastro-intestinale (**hoofdstuk 3**) en genito-urinaire (**hoofdstuk 4**) toxiciteit laten zien dat een toename in dosis op de omliggende organen zal zorgen voor een toename in toxiciteit. De dosis op de urethra in het bijzonder blijkt een sterke invloed te hebben op de genito-urinaire toxiciteit. Het is daarom van belang dat de urethra als risico orgaan wordt meegenomen in het opstellen van het behandelplan en hoge doses op de urethra vermeden worden. De introductie van MRI bij het intekenen

van het doelgebied voor radiotherapie maakt het mogelijk om de urethra in te tekenen. In de FLAME trial werd over het algemeen meer genito-urinaire toxiciteit gezien dan gastro-intestinale toxiciteit (**hoofdstuk 2**). Analyse van het aantal lokale recidieven, regionale- en afstands-metastasen laat zien dat het toevoegen van een focale boost het aantal lokale recidieven halveert en dat het aantal regionale en afstandsmetastasen gecombineerd ook afneemt **(hoofdstuk 5)**. Er werd geen verschil gevonden in afstandsmetastasen, algehele overleving en prostaatkanker specifieke overleving tussen beide studie armen. Ondanks dat er geen verschil werd geobserveerd in afstandsmetastasen in beide studiearmen, werd er wel een dosis-effect relatie gezien tussen de focale boost dosis en de kans op afstandsmetastasen. Een langere follow-up duur zal uitwijzen of dit invloed zal hebben op de kans op afstandsmetastasen en prostaatkanker specifieke overleving in de focale boost arm.

# SCIENTIFIC PUBLICATIONS AND PRESENTATIONS

**Publications**

***Outside of PhD project***

1. Groen VH, Lock MTWT, Keizer B, Horenblas S, Meijer RP. Urothelial carcinoma in an orthotopic neobladder: an unusual pattern of recurrence and metastasis. BMJ Case Rep. 2017 Oct 24;2017:bcr2017221052. doi: 10.1136/bcr-2017-221052. PMID: 29066649; PMCID: PMC5665183.

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3. Groen VH, Lock MTWT, Angst I, Verhagen P, Horenblas S, Dik P et al. Psoas hitch procedure in 166 adult patients: The largest cohort study before the laparoscopic era. BJUI Compass. 2021;2(5):331-337.

***Within PhD project, based on data of the Focal Lesion Ablative Microboost in prostatE cancer (FLAME) trial***

4. Groen VH*, Kerkmeijer LGW*, Pos FJ, Haustermans K, Monninkhof EM, Smeenk RJ, Kunze-Busch M, de Boer JCJ, van der Voort van Zijp J, van Vulpen M, Draulans C, van den Bergh L, Isebaert S, van der Heide UA. 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 Mar 1;39(7):787-796. doi: 10.1200/JCO.20.02873. Epub 2021 Jan 20. PMID: 33471548.

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**Presentations**

1. E-poster at ESTRO conference 2019:
   EP-1556: The effect of an endorectal balloon on GI toxicity after EBRT for localized prostate cancer

2. Oral poster presentation (digital session) at ESTRO conference 2020:
   PH-0114: Dose-volume effects for GI toxicity following EBRT for prostate cancer in the FLAME trial

3. Oral presentation (digital session) at ESTRO conference 2020:
   OC-0315: Quality of life after EBRT with or without focal boost for prostate cancer in the FLAME trial

4. Oral presentation (live session) at ESTRO conference 2021:
   OC-0511: Urethra and bladder dose-effect relations for genitourinary toxicity after EBRT for prostate cancer

5. Interview with OncologyTube: Focal Boost to the Intraprostatic Tumor In External Beam Radiotherapy for Patients With Localized Prostate Cancer March 2021:
   *Veerle Groen, MD from the University Medical Center Utrecht, Radiation Oncology, Utrecht, the Netherlands speaks about Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial.*

# DANKWOORD

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# CURRICULUM VITAE

Veerle Hillegonde Groen was born on the 28th of January, 1993 in Vlaardingen, the Netherlands. In 1996, she moved to Zeist with her parents Jan and Jolanda Groen and her older brother Kasper. After graduating from the Katholieke Scholengemeenschap De Breul, Zeist, in 2011, she moved to Utrecht and attended medical school at the Utrecht University. Veerle gained international experience during clinical internships at the Karapitiya Teaching Hospital (Galle, Sri Lanka) and the Queen Elizabeth Central Hospital (Blantyre, Malawi). Furthermore, she was engaged in educational activities, providing medical training for life-saving interventions at Schok and Pomp and as a student mentor for the Stichting voor Vluchteling Studenten UAF. During her clinical internships, she developed a special interest in the field of Urology. In 2017, she started at the Radiation Oncology Department of the University Medical Center Utrecht, working as a student researcher, addressing the treatment of prostate cancer. After obtaining her medical degree in March 2018, Veerle continued working at the Radiation Oncology Department as a PhD candidate, focusing on focal boosting in external beam radiotherapy for prostate cancer, under guidance of prof.dr. H.M. Verkooijen, prof.dr. U.A. van der Heide, dr. L.G.W. Kerkmeijer and dr. E.M. Monninkhof, which led to this thesis. During her PhD program, she obtained a postgraduate Master of Science degree in Clinical Epidemiology and Medical Statistics at the Utrecht University. Veerle started working as a resident not in training at the Department of Urology at the Jeroen Bosch Hospital in 's-Hertogenbosch in April 2021. In May 2022, she continued her work at the Department of Urology at the University Medical Center Utrecht. In January 2023, she started as surgery resident in training at the Jeroen Bosch Hospital, as part of her residency in Urology. Veerle aspires to be a Urologist that is driven by her passion for research, education, and enhancing healthcare in low-resource environments. Veerle is currently living in Maarssen, the Netherlands, with her partner Marc Vollenbrock.