Phase III randomised trial

Standard whole prostate gland radiotherapy with and without lesion boost in prostate cancer: Toxicity in the FLAME randomized controlled trial

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ABSTRACT

Purpose: To compare toxicity rates in patients with localized prostate cancer treated with standard fractionated external beam radiotherapy (EBRT) with or without an additional integrated boost to the macroscopically visible tumour.

Material and methods: FLAME is a phase 3 multicentre RCT (NCT01168479) of patients with pathologically confirmed localized intermediate or high-risk prostate cancer. The standard treatment arm ($n = 287$) received a dose to the entire prostate of 77 Gy in 35 fractions. The dose-escalated treatment arm ($n = 284$) received 77 Gy in 35 fractions to the entire prostate, with an integrated boost up to 95 Gy to the multi-parametric MRI-defined (macroscopic) tumour within the prostate. Treatment related toxicity was measured using the CTCAE version 3.0. Grade 2 or worse GU or GI events up to two years were compared between groups by presenting proportions and by Generalized Estimating Equations (GEE) analyses for repeated measures.

Results: Ninety percent of the 571 men randomly assigned between September 2009 and January 2015 had high-risk disease (Ash 2000), of whom nearly 66% were prescribed hormonal therapy up to three years. Median follow-up was 55 months at the time of this analysis. Toxicity prevalence rates for both GI and GU increased until the end of treatment and regressed thereafter, with no obvious differences across treatment groups. Late cumulative GI toxicity rates were 11.1% and 10.2% for the standard and dose-escalated group, respectively. These rates were 22.6% and 27.1% for GU toxicity. GEE analyses showed that both GU toxicity and GI toxicity ($\geq$grade 2) up to two years after treatment were similar between arms (OR 1.02 95%CI 0.78–1.33p = 0.81 and (OR 1.19 95%CI 0.82–1.73p = 0.38), respectively.

Conclusions: In intermediate- and high-risk prostate cancer patients, focal dose escalation integrated with standard EBRT did not result in an increase in GU and GI toxicity when compared to the standard treatment up to two years after treatment. This suggests that the described focal dose escalation technique is safe and feasible.

Prostate cancer is the most frequently diagnosed cancer in men and the second most common cause of death due to cancer [1]. External beam radiotherapy (EBRT) is the therapy of choice in the treatment of high-risk disease but has also been shown to have a significant chance of local relapse [2]. To increase efficacy of EBRT

essentially two promising options are being explored, hypofractionation and dose escalation.

Several randomized phase III trials have proven that dose escalation in EBRT benefits outcome in localized prostate cancer. In the Dutch multicentre trial the five-year relapse rate decreased from 46% to 36% with dose escalation up to 78 Gy to the entire prostate, this improvement is persistent with longer follow-up [3,4]. The MRC-RT01 trial compared 64 Gy with 74 Gy and showed ten-year biochemical progression of 57% versus 43% [5]. Dose escalation to 80 Gy in the GETUG-06 trial showed a five-year biochemical

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relapse rate of only 28% compared to 39% for patients treated with 70 Gy [6]. These trials on dose escalation also showed a modest but nevertheless perceptible increase in acute and late toxicity for the escalated-dose treatment that must be weighed against the improved outcome [3,5,6]. In the GETUG-06 trial for example 43% of the patients in the 70 Gy group and 48% of the patients in the 80 Gy group complained of side effects 2 months after the end of treatment [6]. Due to increased toxicity associated with dose escalation, further and substantial dose escalation is not feasible with the techniques currently used. In prostate radiotherapy, current practice is to irradiate the whole organ to the full dose. As local recurrences mainly occur at the site of the primary macroscopic tumour area [7], the next step in increasing the dose could be a focal boost to the macroscopic tumour alone, while electively irradiating the rest of the prostate with the current standard dose [8,9]. This would allow an increase in the tumour dose without increasing the dose to the surrounding healthy tissues. Feasibility of this approach has been shown by adding a low-dose-rate brachytherapy boost to external-beam treatment in a phase 1 study in which three patients were treated with a dose of 95 Gy to the macroscopic tumour within the prostate [10,11].

To investigate the benefit of an ablative microboost to the macroscopic tumour within the prostate, we introduced a randomized controlled trial, the FLAME-trial [12]. The primary endpoint of this trial is to assess whether dose escalation to the multiparametric MRI (mp-MRI)-defined macroscopic tumour up to 95 Gy increases the five-year biochemical progression-free survival (bPFS) rate with acceptable toxicity. Here, we report treatment related side effects up to a time period of two years after the first radiation treatment.

Methods and materials

Study design and patient population

This was a phase 3, single-blind, multicentre randomized controlled trial, comparing standard fractionated EBRT (77 Gy to the whole prostate) to standard fractionation with an additional integrated boost (up to 95 Gy) to the tumour as visible on mp-MRI [12]. The trial was carried out in three centres in the Netherlands, in the University Medical Centre (UMC) Utrecht, the Netherlands Cancer Institute (Amsterdam) and Radboudumc (Nijmegen), and in one centre in Belgium, i.e. University Hospitals Leuven. The study was described in detail elsewhere [12].

In short, patients with intermediate- or high-risk adenocarcinoma of the prostate defined according to the Ash criteria were eligible to participate [13]. Intermediate-risk prostate carcinoma is diagnosed if one of the following factors is present: T2 carcinoma, or the Gleason score = 7, or iPSA is 10–20 ng/mL. A high-risk prostate carcinoma is diagnosed if more than one of these factors is present, or if one or more of the following factors are present: T3 carcinoma, or the Gleason score > 7, or iPSA > 20 ng/mL. Patients with evidence of lymph node involvement or distant metastatic disease, WHO performance score > 2 or IPSS $\geq$ 20 were excluded. Additional exclusion criteria were: Trans Urethral Prostatectomy (TURP) within three months from the start of treatment, prior pelvic radiotherapy, prostatectomy, inability to undergo an MRI exam, or inability to stop with anticoagulant medication prior to placement of fiducial markers.

The trial was approved by the medical ethics committee of the UMC Utrecht in the Netherlands (09-008) and of the University Hospitals Leuven in Belgium (S52698). All patients gave written informed consent.

Radiation therapy

Patients were randomly assigned in a 1:1 ratio by the trial office at the UMC Utrecht, with stratification for centre. Patients are blinded to the actual treatment given until their participation in the study ends after 10 years of follow-up. As the local investigators were treating physicians, masking them to the treatment was not possible.

Patients assigned to the standard treatment received EBRT to a dose of 77 Gy in 35 fractions of 2.2 Gy to the entire prostate. Patients assigned to the dose-escalated treatment received an additional integrated boost to the tumour to a total dose of 95 Gy in 35 fractions of 2.7 Gy. For delineation of target volumes and organs at risk (OAR), CT and mp-MRI exam were performed. MRI exams were scheduled before the start of hormonal therapy and consisted of T2-weighted, diffusion-weighted and dynamic contrast-enhanced MRI. Prior to participation in the trial, each institute submitted their protocol for mp-MRI. The protocols all were consistent with the later published European Society of
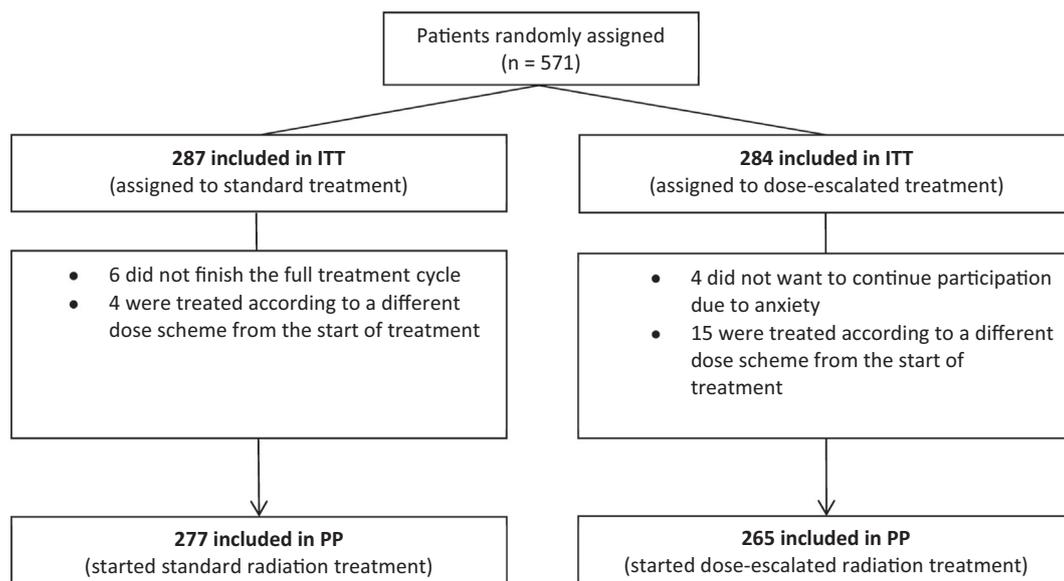

Fig. 1. Trial profile FLAME study.

Table 1
Patient and tumour characteristics at baseline of the FLAME trial.

Baseline (Randomization)	Standard treatment	Dose-escalated treatment
Number of Subjects (*n*)	287	284
Mean age (range)	70 (47–85)	70 (46–83)
Risk stratification (Ash criteria)[*]		
Low-risk	4 (1.4%)	2 (0.7%)
Intermediate-risk	28 (9.8%)	21 (7.4%)
High-risk	255 (88.8%)	261 (91.9%)
Centre	*n* (%)	*n* (%)
UMC Utrecht	160 (55.7)	160 (56.3)
Netherlands Cancer Institute	55 (19.2)	54 (19.0)
University Hospitals Leuven	47 (16.4)	46 (16.2)
Radboudumc	25 (8.7)	24 (8.5)
IPSA (ng/mL)		
Mean (range)	15.2 (0–138)	16.3 (1–100)
Clinical T-stage		
T1c	27 (9.4)	23 (8.1)
T2a	29 (10.1)	28 (9.8)
T2b	18 (6.3)	19 (6.7)
T2c	35 (12.2)	42 (14.8)
T3a	124 (43.2)	111 (39.1)
T3b	45 (15.7)	57 (20.1)
T4	9 (3.1)	4 (1.4)
Biopsy Gleason score		
≤6	55 (19.2)	47 (16.6)
7	139 (48.4)	139 (48.9)
≥ 8	93 (32.4)	98 (34.5)
N-stage		
N0	226 (78.8)	231 (81.3)
pN0 < 10 lymph nodes removed	48 (16.7)	33 (11.6)
pN0 ≥ 10 lymph nodes removed	13 (4.5)	20 (7.1)
Hormonal therapy prescribed		
Yes, 3 years	112 (39.0)	114 (40.1)
Yes, <3 years	77 (26.8)	73 (25.7)
No	98 (34.2)	97 (34.2)
TURP[#]		
Yes	41 (14.3)	36 (12.7)
No	246 (85.7)	248 (87.3)
Cardiovascular disease		
Yes	155 (54.0)	147 (51.8)
No	132 (46.0)	137 (48.2)
Diabetes Mellitus		
Yes	31 (10.8)	30 (10.6)
No	256 (89.2)	254 (89.4)

[*] See Supplementary Table 1 for a comparison of the classification of patients by the ASH D'Amico criteria or NCCN criteria.

[#] >3 months before inclusion.

Urogenital Radiology (ESUR) guidelines [14]. No central reviewing of the gross tumour volume (GTV) was performed.

The seminal vesicles (SV) received a dose according to institutional policy, depending on the risk of involvement, varying from no dose for patients with low risk of SV involvement to 77 Gy for patients with a high risk of involvement. For patients with visible tumour in the SV in the dose-escalated treatment arm, the dose was escalated to 95 Gy if normal tissue dose constraints were not violated. The target volume for dose escalation was defined as all tumour visible on mp-MRI. The planning target volume margin around the prostate was 5–8 mm, dependent on institutional policy. No margin was applied to the dose escalation target volume.

Patients were treated with intensity-modulated radiotherapy (IMRT) (UMC Utrecht) or volumetric arc therapy (VMAT) (University Hospitals Leuven, The Netherlands Cancer Institute, Radboudumc). Local dose constraints for OAR were applied for both the standard and dose-escalated treatment. Additional dose con-

straints of 77 Gy to 1 cc of the rectum and 80 Gy to 1 cc of the bladder were applied. Daily position verification and on-line correction based on implanted fiducial markers were performed [15]. More technical details of the treatment including variations between the institutions can be found in the Supplementary material.

Outcomes

The primary endpoint is five-year bPFS. Biochemical progression is defined as a PSA concentration greater than the nadir plus 2 ng/mL (Phoenix definition), without backdating. Follow-up time at this moment is insufficient to report on the primary endpoint. In this study, we report the treatment-related toxicity within two years.

Patient assessment and follow-up

Patient follow-up was performed weekly during treatment, one month after the last treatment, six months after the start of therapy and annually thereafter. Treatment-related side effects were collected using the Common Toxicity Criteria for adverse events (CTCAE) version 3.0 at baseline and during all follow-up visits. As part of genitourinary (GU) toxicity the following adverse events were scored: urinary frequency/urgency, urinary retention, bladder spasms, urinary incontinence, GU haemorrhage and dysuria. As part of gastrointestinal (GI) toxicity the following adverse events were scored: rectal or perirectal pain, proctitis, diarrhoea, flatulence, haemorrhoids, anal incontinence, rectal fistula and rectal haemorrhage.
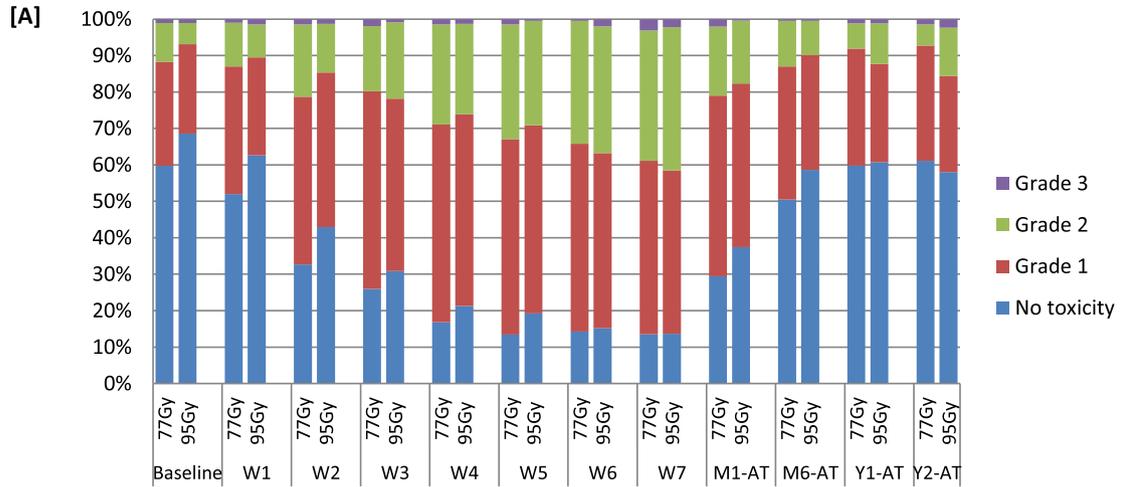
Statistical analysis

The sample size for the FLAME study was calculated on the primary endpoint five-year bPFS. We estimated that the standard treatment would result in a five-year bPFS of 64% [3]. A one-sided hypothesis was used since an increase in biochemical failure is not expected upon focal dose escalation. The hypothesis was to detect a 10% increase in five-year bPFS in the dose-escalated treatment group; and with a power of 80% and a 5% significance level, we established that 283 patients would be needed per treatment arm.

Primary analyses were performed on an intention-to-treat basis (ITT). This means that all patients who were randomized were included for analysis, regardless of whether they received radiotherapy according to protocol or not. Additionally, we performed per protocol analyses excluding patients who did not receive the assigned treatment or were withdrawn from participation in the dose-escalation arm due to anxiety for potential toxicity (Fig. 1).

Toxicity scores were presented up to 2 years after the first radiation treatment as a function of time. A comparison in toxicity scores between the dose-escalated treatment group and the standard treatment group was made using the following approaches. First, we descriptively showed the prevalence of GU and GI toxicity scores for each time point. Second, we compared the acute (during treatment) and late (from 3 months after start of treatment to 2 years after treatment) cumulative prevalence of grade 2 or worse GU or GI events by presenting the difference + corresponding 95% confidence intervals (CIs). Third, we compared the prevalence of grade 2 or worse GU or GI events up to two years after treatment over time by graphical display and GEE analyses for dichotomous outcomes. The GEE analyses were repeated on the per protocol dataset.

To account for missing data, multiple imputation was used for the GEE analyses and a sensitivity analysis for the plots of the prevalence of grade 2 or worse GU or GI events [16,17]. With multiple imputation, the incomplete dataset is replicated multiple

[A]

% missing scores	Baseline	W1	W2	W3	W4	W5	W6	W7	M1-AT	M6-AT	Y1-AT	Y2-AT
77Gy	2	30	30	26	31	32	32	33	17	30	14	28
95Gy	4	29	21	23	19	25	28	36	11	29	11	25

[B]
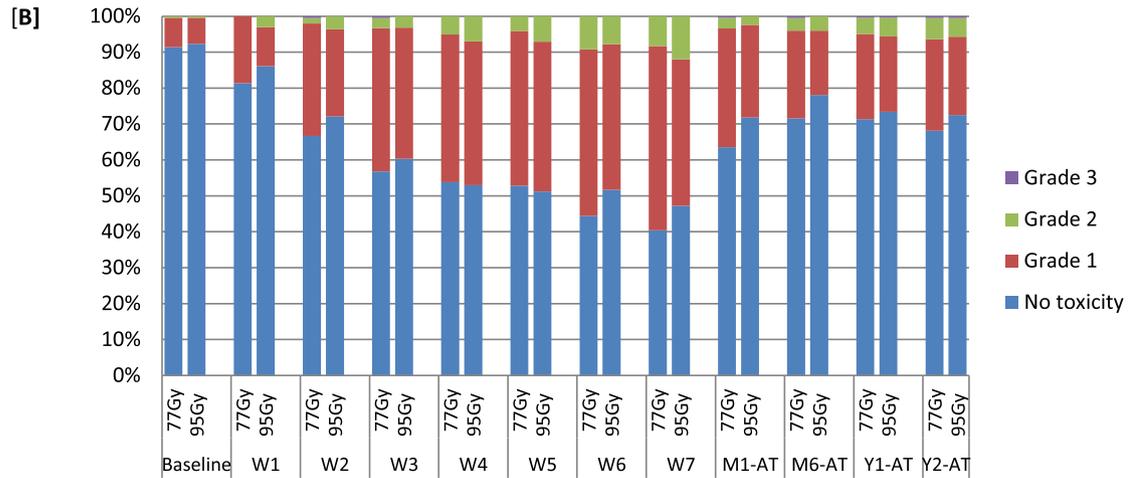
% missing scores	Baseline	W1	W2	W3	W4	W5	W6	W7	M1-AT	M6-AT	Y1-AT	Y2-AT
77Gy	2	31	30	26	31	32	32	33	18	30	15	29
95Gy	4	29	22	23	19	26	28	35	11	29	11	26

W = week ; M = month; Y = year; AT = After Treatment

GU = genitourinary

GI = gastrointestinal

Fig. 2. Toxicity scores in the dose-escalated treatment arm and standard treatment arm per time point. [A] Prevalence of GU toxicity scores (%) and missing GU toxicity scores per time point. [B] Prevalence of GI toxicity scores (%) and missing GI toxicity scores per time point.

times whereby the missing data in each set are replaced with plausible values drawn from an imputation model. Thereafter, the statistical analysis is performed on each imputed dataset separately. Finally, the estimates from all datasets are combined using 'Rubin's rules' [18]. In our analysis, we used all baseline variables as seen in Table 1 as well as the (overall) GI and GU toxicity scores for the imputation model and created ten imputed datasets. Statistical analysis was performed using SPSS version 23.0 software. A two-sided P-value < 0.05 was considered statistically significant.

Results

Between September 2009 and January 2015, 571 patients were enroled and randomly assigned to the standard or dose-escalated treatment. In total, 287 patients were assigned to the standard treatment and 284 patients to the dose-escalated treatment. Baseline characteristics were evenly distributed between the two groups and are reported in Table 1. According to the Ash criteria for risk classification, 89% of patients in the standard arm and

92% of the patients in the dose-escalated arm had high-risk disease (see Table 1). Since risk assignment according to D'Amico criteria or the National Comprehensive Cancer Network (NCCN) criteria is more common these days, we also classified the study population according to these criteria (see Supplemental Table S2). Nearly 66% of the high risk patients were prescribed some form of hormonal therapy: 26% shorter than 3 years and 40% 3 years. Median follow-up was 55 months at the time of this analysis.

Patients included in the per protocol analyses are listed in Fig. 1. In total, 277 patients (97%) of the standard treatment arm and 265 patients (93%) of the dose-escalated arm were included. In the standard treatment arm, six patients were excluded because they did not finish the full treatment scheme and four patients were treated according to a different dose scheme from the start of treatment. Four patients did not want to participate after being randomised in the dose-escalated arm due to anxiety for potential toxicities. Furthermore, 15 patients in the dose-escalated arm were treated according to a different dose scheme from the start of treatment. Reasons for treatment according to a different dose scheme included; claustrophobia, exceeded dose on organs at risk and undetectability of the tumour on MRI.

The mean dose delivered to the mp-MRI defined tumour in the dose-escalated arm was 91.9 Gy ± 3.6 Gy. The near maximum dose (D1cc) to the rectum was 74.2 ± 1.2 Gy in the standard treatment arm and 74.4 ± 3.5 Gy for the dose-escalated arm. The near maximum dose to the bladder was 75.5 ± 2.7 Gy and 76.3 ± 3.7 Gy in the standard and study arm, respectively. The median volume (10–90 percentile) of the GTV in the dose-escalated group was 2.9 cm^3 (0.7–9.4 cm^3).

Analysis of patterns of missing data showed that the missing toxicity scores were slightly higher in the standard dose arm (26%) compared to the dose-escalated arm (22%).

The prevalence of all toxicity grades is shown in Fig. 2 and the prevalence of grade $\geq$ 2 GU and GI events over time are depicted in Fig. 3. Toxicity prevalence's for both GI and GU increased until the end of treatment and regressed thereafter, with no obvious differences across treatment groups. In the sensitivity analyses, Fig. 3 did not materially change after imputation of missing data (Fig. S1). Acute and late cumulative toxicity scores for both treatment arms are depicted in Table 2. Acute GI toxicity rates were 10.1% and 14.8% for the standard and dose-escalated group, respectively. These rates were 46.0% and 42.3% for GU toxicity. Late cumulative GI toxicity rates were 11.1% and 10.2% for the standard and dose-escalated group, respectively. These rates were 22.6% and 27.1% for GU toxicity. Differences in acute and late cumulative toxicity were not statistically significantly different between treatment groups.

The GEE analyses, using the imputed data, showed that the prevalence of $\geq$grade 2 GU toxicity over time was similar across arms (pooled OR 1.02 95%CI 0.782–1.33p = 0.81). The pooled odds for $\geq$grade 2 GI toxicity was not significantly different between the groups either (pooled OR 1.19 95%CI 0.82–1.73p = 0.38). There were no patients with grade 4 toxicity up to two years of follow-up. Per protocol analyses showed similar results of the prevalence of $\geq$grade 2 toxicities (pooled OR $\geq$ grade 2 GU 1.06, 95% CI 0.80–1.39 and 1.22, 95% CI 0.84–1.79 for $\geq$grade 2 GI, respectively).

Discussion

On the basis of our findings an integrated boost up to 95 Gy to the mp-MRI based intraprostatic lesion is feasible and does not result in a significant increase in toxicity up to two years. An explanation of the similarity in toxicity profile for both treatment arms can be found in the technical administration of the irradiation and
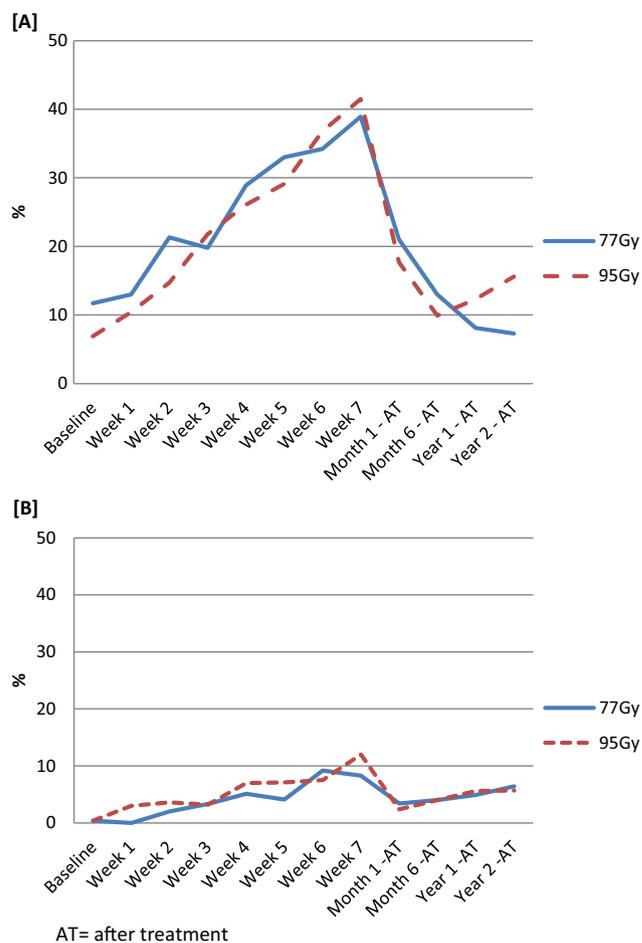
Fig. 3. Toxicity scores as a function of time. Comparison between the dose-escalated treatment arm and the standard treatment arm regarding. [A] Prevalence of grade 2 or worse GU events. [B] Prevalence of grade 2 or worse GI events.

the delivered doses to rectum and bladder. Dose constraints and subsequently the planned near maximum doses to the rectum and bladder did not differ between both arms. Any significant differences in dose to organs at risk may arise from inter- and intra-fraction movement; therefore, the position verification protocol can be expected to play an important role to adequately compensate movement. Despite position verification, inter and intrafraction movements still may have caused differences in rectal and bladder dose between the treatment arms, although the similarity in observed toxicity so far does not indicate this is the case.

Since the urethra was not delineated and no constraints were set, patients treated in the dose-escalated treatment arm may have received a higher dose to the urethra. As a consequence, increased fibrosis of the urethra may take place, eventually leading to strictures and urinary retention. While this still may emerge at later time points, up to now, no significant differences in urethra-related toxicity can be noted.

The FLAME approach can also be considered a mild form of hypofractionation, where the prostate receives 2.2 Gy/fraction and the tumour 2.7 Gy/fraction. When compared with recent hypofractionation trials, the FLAME trial shows toxicity rates in a similar range. The CHHiP trial randomized patients to conventional (74 Gy delivered in 37 fractions over 7.4 weeks) or one of two hypofractionated schedules (60 Gy in 20 fractions over 4 weeks or 57 Gy in 19 fractions over 3.8 weeks) all delivered with intensity-modulated techniques conventional radiotherapy [19]. A preliminary safety analysis of the CHHiP trial after 50.5 months

Table 2
Comparison of acute and late cumulative toxicity events between the treatment groups.

	Gastrointestinal (GI) toxicity			Genitourinary (GU) toxicity		
	Standard arm (%)	Dose-escalation (%)	Treatment difference[*] +95% CI (%)	Standard (%)	Dose-escalation (%)	Treatment difference[*] +95% CI (%)
Acute toxicity	10.1	14.8	4.7 (−0.7 *to* 10.09)	46.0	42.3	−3.7 (−11.9 *to* 4.4)
Late toxicity	11.1	10.2	−0.9 (−6.0 *to* 4.1)	22.6	27.1	4.5 (−2.6 *to* 11.6)

Acute toxicity = during radiotherapy treatment.
Late toxicity = from 1 month to 2 years after treatment.
[*] % Dose-escalation arm -% standard arm.

of median follow-up showed that at 2 years of following 60 Gy in 20 fractions, 3.6% of the men had RTOG scale GI toxicity ≥ grade 2 and 2.2% RTOG scale GU toxicity ≥ grade 2 [20]. The HYPRO trial [21,22] randomized patients to receive either standard fractionation with 39 fractions of 2 Gy in 8 weeks (five fractions per week) or hypofractionation with 19 fractions of 3.4 Gy in 6.5 weeks (three fractions per week). For the hypofractionation arm, the reported cumulative incidence of ≥grade 2 GU acute and late (at 3 years) toxicity was 23% and 41.3%, respectively. The cumulative incidence for ≥grade 2 GI acute and late toxicity (3 years) was 13.0% and 17.7%, respectively.

Although a direct comparison of the toxicity data of the different trials is complicated because of differences in toxicity scoring and reporting, differences in patient selection etc., it shows that the toxicity data of the FLAME trial are reasonable, even with a much higher total dose of 95 Gy to the tumour. An advantage of the FLAME trial was that it involved standard fractionation with an additional integrated boost to the macroscopically visible tumour, so that the dose to the OAR remained unchanged relative to the standard treatment.

Earlier (single arm) trials indicated that an integrated boost to the intraprostatic lesion (up to 90 Gy) can be delivered safely and seem to further improve (biochemical) outcome [9,23,24]. A disadvantage of these single arm trials is the possibility of selection bias. It is, therefore, important that definitive results on clinical outcomes from randomized trials such as the FLAME will become available shortly.

A shortcoming of the FLAME trial is the relatively high rate of missing toxicity data. Nonetheless, we do not expect that this has an impact on the validity of the results since we used multiple imputation techniques and a prevalence toxicity plot of the raw data up to two years after treatment did not materially differ from a plot including the imputed data. Furthermore, for the primary endpoint of the trial (five-year bPFS), the missing toxicity data have no impact as collection of PSA data has continued according to protocol.

Another limitation is that baseline imaging investigations were not protocolled for study inclusion in the FLAME trial. In practice, the mp-MRI exam required for tumour delineation was done mostly before randomization. In some cases however, for logistical reasons the choice was made to image patients within the context of radiation preparation (CT- and MRI-scan) after randomization occurred. Drawback of this procedure was indeed that these scans could reveal unexpected metastases, which was the case in a small number of patients (n = 5). In a limited number of patients (n = 11), no tumour could be identified on mp-MRI, resulting in a treatment according to the standard arm. Furthermore, contrary to the inclusion criteria, six patients with low risk disease were randomized. We do not expect this to have an impact on toxicity.

While the clinical benefit of focal dose escalation still needs to be established, a dose of up to 95 Gy to the intraprostatic lesion does not increase genitourinary and gastrointestinal toxicity up to two years. This indicates that the described focal dose escalation technique can be safely performed in routine daily practice in patients with local intermediate- and high-risk prostate cancer.

Registration number ClinicalTrials.gov

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Conflict of interest statement

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2017.12.022.

References

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
[2] Zelefsky MJ, Eastham JA, Cronin AM, Fuks Z, Zhang Z, Yamada Y, et al. Metastasis after radical prostatectomy or external beam radiotherapy for patients with clinically localized prostate cancer: a comparison of clinical cohorts adjusted for case mix. J Clin Oncol 2010;28:1508–13.
[3] Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol 2006;24:1990–6.
[4] Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MF, Lebesque JV. Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. Radiother Oncol 2014;110:104–9.
[5] Dearnaley DP, Jovic G, Syndikus I, Khoo V, Cowan RA, Graham JD, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. Lancet Oncol 2014;15:464–73.
[6] Beckendorf V, Guerif S, Le PE, Cosset JM, Bougnoux A, Chauvet B, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys 2011;80:1056–63.
[7] Chopra S, Toi A, Taback N, Evans A, Haider MA, Milosevic M, et al. Pathological predictors for site of local recurrence after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2012;82:e441–8.
[8] Fonteyne V, Villeirs G, Speleers B, De NW, De WC, Lumen N, et al. Intensity-modulated radiotherapy as primary therapy for prostate cancer: report on acute toxicity after dose escalation with simultaneous integrated boost to intraprostatic lesion. Int J Radiat Oncol Biol Phys 2008;72:799–807.
[9] Miralbell R, Molla M, Rouzaud M, Hidalgo A, Toscas JI, Lozano J, et al. Hypofractionated boost to the dominant tumor region with intensity modulated stereotactic radiotherapy for prostate cancer: a sequential dose escalation pilot study. Int J Radiat Oncol Biol Phys 2010;78:50–7.
[10] Singh AK, Guion P, Sears-Crouse N, Ullman K, Smith S, Albert PS, et al. Simultaneous integrated boost of biopsy proven, MRI defined dominant intra-prostatic lesions to 95 Gray with IMRT: early results of a phase I NCI study. Radiat Oncol 2007;2:36.

[11] Ellis RJ, Zhou H, Kaminsky DA, Fu P, Kim EY, Sodee DB, et al. Rectal morbidity after permanent prostate brachytherapy with dose escalation to biologic target volumes identified by SPECT/CT fusion. Brachytherapy 2007;6:149–56.

[12] Lips IM, van der Heide UA, Haustermans K, van Lin EN, Pos F, Franken SP, et al. Single blind randomized phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial): study protocol for a randomized controlled trial. Trials 2011;12:255.

[13] Ash D, Flynn A, Battermann J, de,. RT, Lavagnini P, Blank L. ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. Radiother Oncol 2000;57:315–21.

[14] Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. Eur Radiol 2012;22:746–57.

[15] Moman MR, van der Heide UA, Kotte AN, van Moorselaar RJ, Bol GH, Franken SP, et al. Long-term experience with transrectal and transperineal implantations of fiducial gold markers in the prostate for position verification in external beam radiotherapy; feasibility, toxicity and quality of life. Radiother Oncol 2010;96:38–42.

[16] Groenwold RH, Donders AR, Roes KC, Harrell Jr FE, Moons KG. Dealing with missing outcome data in randomized trials and observational studies. Am J Epidemiol 2012;175:210–7.

[17] Groenwold RH, Moons KG, Vandenbroucke JP. Randomized trials with missing outcome data: how to analyze and what to report. CMAJ 2014;186:1153–7.

[18] Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Med Res Methodol 2009;9:57.

[19] Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2016;17:1047–60.

[20] Dearnaley D, Syndikus I, Sumo G, Bidmead M, Bloomfield D, Clark C, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. Lancet Oncol 2012;13:43–54.

[21] Aluwini S, Pos F, Schimmel E, Krol S, van der Toorn PP, de JH,, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised, non-inferiority, phase 3 trial. Lancet Oncol 2016;17:464–74.

[22] Aluwini S, Pos F, Schimmel E, van LE, Krol S, van der Toorn PP,, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. Lancet Oncol 2015;16:274–83.

[23] Ippolito E, Mantini G, Morganti AG, Mazzeo E, Padula GD, Digesu C, et al. Intensity-modulated radiotherapy with simultaneous integrated boost to dominant intraprostatic lesion: preliminary report on toxicity. Am J Clin Oncol 2012;35:158–62.

[24] Sundahl N, De MG, Villeirs G, Ost P, De NW, Lumen N, et al. Combining high dose external beam radiotherapy with a simultaneous integrated boost to the dominant intraprostatic lesion: analysis of genito-urinary and rectal toxicity. Radiother Oncol 2016;119:398–404.