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Original Article

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

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ABSTRACT

Background and 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).

Material 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.

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

Abbreviations: FLAME, Focal Lesion Ablative Microboost in Prostate Cancer; EBRT, External Beam Radiation Therapy; GI, Gastrointestinal; OAR, Organs At Risk; bDFS, biochemical Disease-Free Survival; mpMRI, multiparametric Magnetic Resonance Imaging; EAU, European Association of Urology; TURP, Trans Urethral Resection of the Prostate; GTV, Gross Tumor Volume; PTV, Planning Target Volume; CTV, Clinical Target Volume; CTCAE, Common Terminology Criteria for Adverse Events; IQR, Interquartile Range; OR, Odds Ratio.

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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 at least one of the following factors: ≥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 additional integrated additional 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 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% ≥72 Gy, ≤50% ≥50 Gy, 1 cm^3 ≤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, patient were reviewed each week at the treating physician. Follow-up consisted of appointments with the physician 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 symtoms 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 locoregional 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 Fig. 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).

The prevalence of GI toxicity increased during treatment, normalized one month after treatment, and increased again in the first two years after treatment (Fig. 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 Fig. 3.

We carried out a separate model to investigate the association between acute and late GI toxicity and found that acute GI toxicity

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%
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%

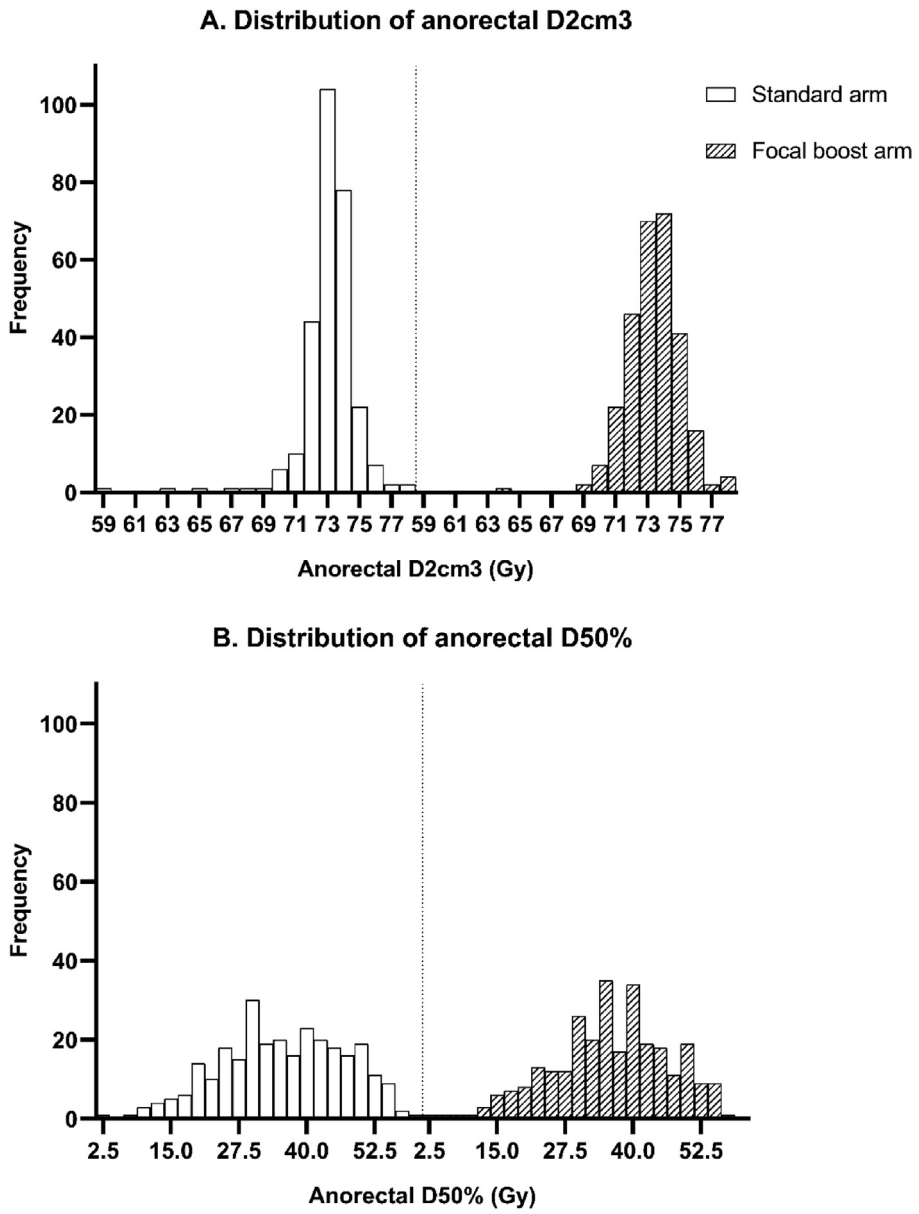


Fig. 1. Histogram of planned dose to the anorectum per treatment arm. A. D2cm^3 and B. D50%.

was associated with late GI toxicity with an OR of 2.58 (95% CI 0.52–12.85, p = 0.25).

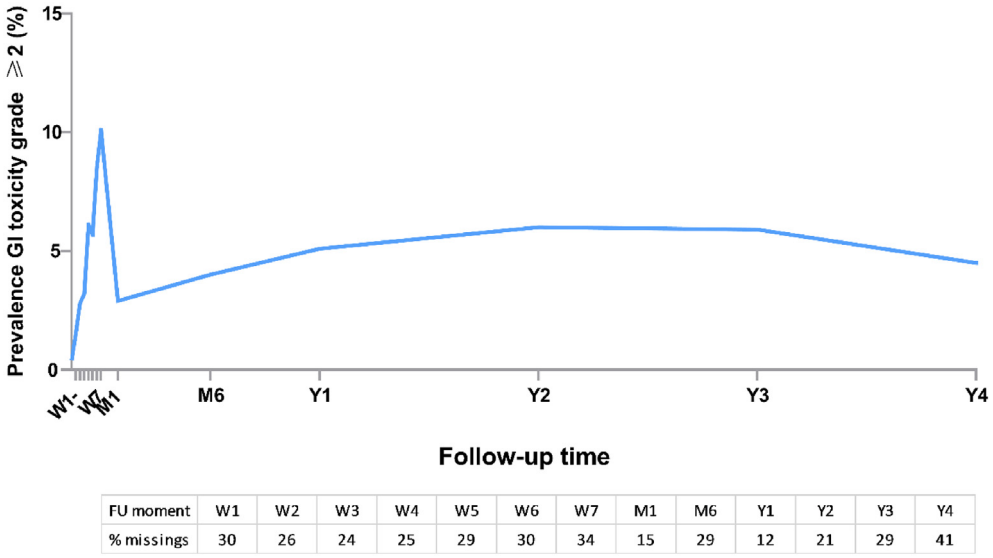
Discussion

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



FU moment	W1	W2	W3	W4	W5	W6	W7	M1	M6	Y1	Y2	Y3	Y4
% missings	30	26	24	25	29	30	34	15	29	12	21	29	41

Fig. 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.

Table 2
The cumulative incidence of GI toxicity grade ≥2 based on raw data. The association between anorectum dose and GI toxicity: results of generalized linear mixed models with and without adjustment for potential confounding factors for GI toxicity.

	Overall GI toxicity grade ≥2		Proctitis grade ≥2	Rectal pain grade ≥2	Fecal incontinence grade ≥2	Diarrhea grade ≥2	Rectal bleeding grade ≥2
Acute toxicity	13% (95% CI 11–16% n = 75)		5% (95% CI 3–7% n = 26)	2% (95% CI 1–4% n = 12)	1% (95% CI 0–2% n = 4)	4% (95% CI 3–6% n = 22)	1% (95% CI 0–1% n = 3)
Late toxicity	12% (95% CI 9–15% n = 67)		5% (95% CI 3–7% n = 28)	0% (95% CI 0–1% n = 2)	2% (95% CI 1–3% n = 11)	0% (95% CI 0–1% n = 1)	4% (95% CI 2–6% n = 21)
Cumulative toxicity	22% (95% CI 19–26% n = 128)		9% (95% CI 7–11% n = 49)	3% (95% CI 1–4% n = 14)	3% (95% CI 2–4% n = 15)	4% (95% CI 3–6% n = 23)	4% (95% CI 3–6% n = 24)
	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)					
Rectal D2cm^3	1.15 (1.12–1.19, p < 0.0001)	1.17 (1.13–1.21, p < 0.0001)					
Rectal D50%	1.16 (1.12–1.21, p < 0.0001)	1.20 (1.14–1.25, p < 0.0001)					

*The ORs for the dose parameters mean that when the planned dose to the D2cm^3 and the D50% of the anorectum increases with 1 Gy, the odds of developing GI toxicity grade ≥2 increase with the corresponding given OR.

were associated with increased late GI toxicity [27,28]. Additionally, associations with intermediate-high dose regions (30–50 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 D2cm^3 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 adjusting for center.

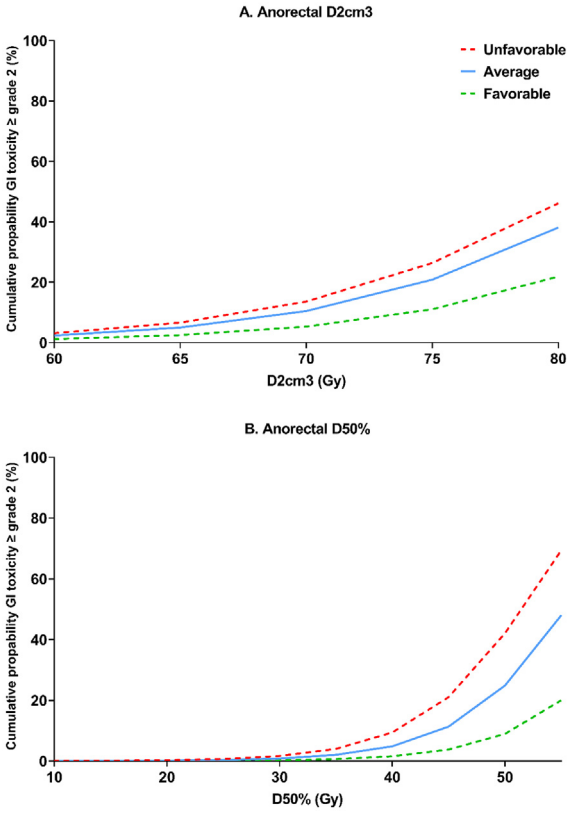


Fig. 3. Dose–toxicity curves of the probability of late cumulative GI toxicity grade ≥2 related to the planned dose based on the generalized linear mixed effects models adjusted for age, T-stage, hormonal therapy, diabetes mellitus, cardiovascular diseases, baseline GI toxicity grade ≥1 (average probability of GI toxicity). 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).

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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Conflict of interest statement

All authors declare having no conflict of interest related to the content of this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.06.033.

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