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Original Article

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ABSTRACT

Introduction: The FLAME trial demonstrated that the dose to the gross tumor volume (GTV) is associated with tumour control in prostate cancer patients. This raises the question if dose de-escalation to the remaining prostate gland can be considered. Therefore, we investigated if intraprostatic recurrences occur at the location of the GTV and which dose was delivered at that location.

Materials and methods: For FLAME trial patients with an intra-prostatic recurrence, we collected pre-treatment images, GTV delineations, dose distributions and post-recurrence images. Pre-treatment images were registered to the post-recurrence images (PSMA-PET CT). An overlap between GTV and PSMA-PET activity was considered an intra-prostatic recurrence at the location of the primary tumor.

Results: Twenty eight out of 535 patients in the FLAME trial had an intra-prostatic recurrence. Its location could be determined for 24 patients. One patient recurred in the prostate gland outside the GTV. The median near-minimum dose to the GTV (D98%) was 76.5 Gy (range: 73.3–86.5 Gy). Only one patient with a recurrence in the GTV received a substantial focal boost of 86.5 Gy. The D98% of all remaining patients was < 81 Gy.

Conclusion: Intra-prostatic recurrences of intermediate- and high-risk prostate cancer patients treated with radiotherapy appeared predominantly at the location of the primary tumor. All but one patient did not receive a high dose to the GTV. Intra-prostatic failure is likely a consequence of the undertreatment of the primary tumor rather than the undertreatment of the remaining prostate gland.

Introduction

Up until recently, radiotherapy for localized prostate cancer considered the whole prostate gland to be the main target for irradiation. In an effort to improve the therapy outcome, the treatment dose to the prostate gland has been increased over the years. Due to the low alpha–beta ratio of prostate carcinoma, strategies such as hypofractionation have been implemented to further intensify the treatment while balancing the side effects [1]. However, due to the close proximity of organs-at-risk, such as bladder and rectum, further dose escalation to the whole prostate gland without an increase in toxicity becomes challenging [2]. The FLAME trial demonstrated that dose escalation to the primary tumor significantly improves the 5-year biochemical disease-free survival without any additional toxicity [3,4]. This was achieved by prioritizing the organs-at-risk constraints over the focal boost dose which resulted in a reduced dose to the primary tumor for some patients in the focal boost arm [5]. Further analysis of the trial data showed that there might be potential to further improve outcome if a high focal boost could be delivered [6].

In the FLAME trial, a clear dose–effect relationship was observed that

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links the near-minimum dose to the gross tumor volume (GTV) to the observed outcome [3]. Hence, while focal boosting maintains a high tumor control, we might consider if treatment-related toxicities could be reduced by de-escalating the dose to the remaining prostate gland, which is defined routinely as clinical target volume (CTV). As a first step towards this strategy, we need to investigate where intra-prostatic recurrences occur in the prostate gland. An analysis of the location of intra-prostatic recurrence without the context of focal boosting was previously done by Cellini et al., Arraye et al. and Pucar et al. in relatively small cohorts (<13 patients) [7,8,9]. Their findings suggest that intra-prostatic recurrences appear mostly at the location of the primary tumor. This claim was further confirmed in a recent study by Gorovets et al. who showed that the presence of a dominant lesion was strongly associated with intra-prostatic recurrence with the location of recurrence being within that dominant lesion [10]. These studies further conclude that their results support the rationale behind treatment intensification at the location of the primary tumor. Hence, a similar analysis in a cohort of patients who underwent such a treatment is warranted.

In this study, we investigated the location and dosimetry of intra-prostatic recurrences in the intermediate- and high-risk FLAME cohort. Using this cohort for the analysis expatiates on the current knowledge by analyzing outcome after a focal boost treatment. We aim to determine if intra-prostatic recurrences after radiotherapy with an integrated focal boost originate from an undertreated primary tumor or undertreated CTV. In the future, this could be used as a premise for refinement of the focal boosting approach, potentially resulting in reduced treatment-related toxicities without compromised outcome.

Materials & methods

Patient population

The FLAME trial investigated the benefit of focal boosting in patients with localized prostate cancer [3]. Intermediate- and high-risk prostate center patients were recruited in four centers (the University Medical Center Utrecht, the Netherlands Cancer Institute and Radboud University Medical Center Nijmegen in The Netherlands and the University Hospitals Leuven in Belgium) with the approval from medical ethics committees of the University Medical Center Utrecht in the Netherlands (NL26038.041.08) and of the University Hospitals Leuven in Belgium (B322201110225). Patients were randomized in between a control arm (77 Gy over 35 fractions to the whole prostate gland) and a focal boost arm (control treatment with an additional focal boost of up to 95 Gy to the GTV). Written informed consent was collected from all patients.

Data set

Our analysis focused on all patients from the FLAME trial who presented with intra-prostatic recurrences (recurrence within the prostate gland and/or seminal vesicles). An intra-prostatic recurrence was determined based on imaging which was often indicated due to biochemical failure (prostate-specific antigen (PSA) nadir + 2 ng/mL) recorded at a follow-up. Clinical characteristics and treatment information were collected for each patient. We retrieved pre-treatment images including GTV and clinical target volume (CTV) delineations and the radiotherapy dose distribution. The pre-treatment images consisted of planning CT, T2-weighted MRI, diffusion weighted MRI and Dynamic Contrast-Enhanced MRI. Pre-treatment GTV delineations were done using this set of multiparametric MRI. In case GTV delineations were not available which could occur in the control arm of the trial, they were delineated afterwards by an experienced uro-radiologist using the same set of pre-treatment images. The images made after the detection of recurrence, prostate-specific membrane antigen positron emission tomography combined with CT (PSMA-PET CT) and/or MRI, were collected from the trial centers.

Intra-prostatic recurrence analysis

The CT component of the PSMA PET CT made after recurrence, was rigidly registered to the planning CT while being blinded to the primary GTV and to the PSMA signal. The registration was verified using fiducial markers. In case PSMA-PET CT images were not available and MRI was used to identify the location of recurrence, we rigidly registered T2-weighted images acquired after the moment of recurrence to the pre-treatment T2-weighted images. The schematic of image processing is shown in Fig. 1.

The location of the intra-prostatic recurrence was identified as an increased metabolic activity on PSMA-PET. The setting of the window-level of standardized uptake value was optimized for the best possible interpretation at the discretion of the observer. A nuclear medicine physician defined a contour based on the PSMA-PET signal within these settings. In case PSMA-PET images were not conclusive or not available, MRI was used to identify the recurrence location. In such a case, a recurrence was defined as a location of MRI conspicuity (low T2 weighted signal and low apparent diffusion coefficient (ADC) signal). No margins were applied for both PSMA-PET and MRI-based contours. A recurrence at the location of the primary GTV in the prostate gland was defined as an overlap between the GTV delineation in the pre-treatment images and the recurrence location based on the images made after the detection of recurrence. A recurrence in the seminal vesicles was considered to be at the location of the primary GTV if there was prior seminal vesicle involvement visible on the pre-treatment scans.

Dosimetric analysis

The FLAME trial implemented an *iso*-toxic focal boosting strategy which meant that the organs-at-risk dose constraints were prioritized over the treatment dose. This led to deviations from the intended dose in the focal boost arm. Hence, the actual planned dose for each patient was acquired from the radiotherapy plan. The near minimum dose to the GTV (D98%) was calculated for each patient. In case of multiple foci, the minimum D98% over all GTVs was reported.

Results

The median follow-up of the FLAME cohort was 5.0 (IQR: 4.8–7.2) years. As previously reported by Groen et al., from 535 per protocol patients in the FLAME trial, 28 recurred within the prostate gland and/or seminal vesicles; 21 in the control arm and 7 in the focal boost arm [11]. This was established based on post-treatment imaging which was done in 89 of 97 patients who presented with clinical failure. Four out of eight patients were not imaged due to death occurring within 6 months of first recorded recurrence. One patient could not be imaged due to his medical condition. The cause for post-recurrence imaging not been done was unknown for the remaining three patients. Table 1 shows the clinical characteristics of patients with intra-prostatic recurrence. The median failure time was 4.8 years (range: 1.7 – 7.4 years). Twelve patients with intra-prostatic recurrence also recurred in the lymph nodes and eight had distant metastases. Three patients who presented with intra-prostatic recurrence eventually died of disease-related cause.

Pre-treatment images were available for all patients. Four patients in the control arm had missing GTV delineations and were therefore additionally delineated by an experienced uro-radiologist. Post-recurrence images were collected for 24 patients from which 23 patients had PSMA-PET CT available. The voxel size of PSMA-PET slightly varied across institutes and time, but the most commonly used resolutions were 4.1x4.1x3.0 mm (11) and 4x4x4 mm (10). One patient had an MRI scan only. Post-recurrence images could not be retrieved for four patients from the referring centers. A flowchart describing the images used for analysis is shown in Fig. 2.

Confirmation of the location of the intra-prostatic recurrence by imaging or biopsy was possible in all patients for whom the post-

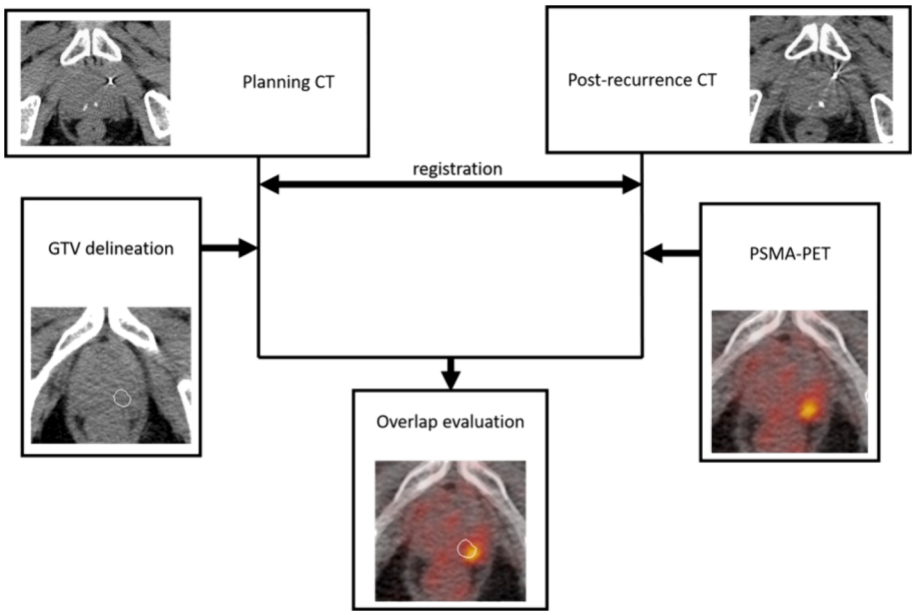

Fig. 1. Image processing steps. Planning CT and the CT made after recurrence were rigidly registered and fiducial markers were used to adjust and verify the final position. Then, primary GTV delineations were displayed on the planning CT as well as PSMA signal on the CT from the moment of recurrence. Finally, the overlap of these two locations was inspected and evaluated by a radiation oncologist. In case PSMA-PET CT images were not available or inconclusive, MRI images or biopsy mappings were used to identify the location of recurrence.

Table 1
Clinical characteristics of patients with intra-prostatic recurrence. Continuous variables are presented as mean and standard deviation if normally distributed, otherwise as median and interquartile range (IQR), or range. Categorical variables are presented as an absolute number and percentage. (ISUP GG=International Society of Urological Pathology grade group [24]; GTV=gross tumor volume).

	Intra-prostatic recurrence cohort N=28
Dose D98% [Gy]	76.5 (range: 73.3 – 86.5)
Age [years]	67 (SD: 60—73)
Prostate specific antigen [ng/mL]	13.0 (IQR: 9.1—22.0)
ISUP GG	
ISUP GG 1 (%)	3 (10.7 %)
ISUP GG 2 or 3 (%)	15 (53.6 %)
ISUP GG 4 or 5 (%)	10 (35.7 %)
T-stage	
T-stage $\leq$ T2 (%)	8 (28.6 %)
T-stage T3a (%)	12 (42.9 %)
T-stage $\geq$ T3b (%)	8 (28.6 %)
Hormone therapy	
None (%)	11 (39.3 %)
$\leq$ 6 months (%)	3 (10.7 %)
6–18 months (%)	4 (14.3 %)
18–36 months (%)	10 (35.7 %)
Neoadjuvant hormone therapy (%)	1 (3.6 %)
Pre-treatment number of GTV(s)	
1	18 (64 %)
2	8 (29 %)
3	2 (7 %)

recurrence images could be retrieved. There was one patient with inconclusive PSMA-PET due to a high intensity signal around the transurethral resection cavity. For this patient however, the location of recurrence could be determined based on MRI scans. Additionally, for the patient who had only post-recurrence MRI scans available, it was initially not possible to identify the exact location of the intra-prostatic recurrence. This was due to the MRI scans being inconclusive. However, biopsy results with T2-weighted images of the biopsy needle placement were available. A biopsy sample taken from the location of the primary GTV was found positive, with 50 % of the core being cancerous.

Overall, 23 patients (23/24, 96 %) recurred at the location of a primary GTV. Twenty-one patients relapsed in the prostate gland and two in the seminal vesicles. An example of a subset of the intra-prostatic recurrences is shown in Fig. 3. Twenty one of these patients had only one location of intra-prostatic recurrence. Two patients might have also recurred at an additional location inside the prostate gland. For one of these patients, the second recurrence location was in the close proximity to the primary GTV (a borderline overlap). Hence, it was not possible to conclude if this was a new focus or if this PSMA-PET activity also originated from the primary GTV. For the other patient, there was a discordance in GTV identification in the pre-treatment images. The new focus lied at a location which was described as potentially malignant on the pre-treatment imaging report. However, this location was not found suspicious upon review by an uro-radiologist.

For one patient (1/24, 4 %), the single intra-prostatic recurrence appeared solely outside of the primary GTV at the location of the anterior fibromuscular stroma. At this location it is difficult to distinguish between tumor and healthy tissue on MRI as they both have a low intensity signal in both T2-weighted MRI and ADC scan. Moreover, this location is also difficult to reach with biopsies. The pre-treatment images as well as the post-recurrence images are shown in Fig. 4.

The mean near-minimum dose to the GTV of patients who presented with intra-prostatic recurrence was 76.5 Gy (range: 73.3 – 86.5 Gy). The patient who recurred at a new location was treated with D98% of 80.7 Gy to the GTV, but the D98% at the location of the intraprostatic recurrence in the CTV was 76.5 Gy. There was only one patient with intra-prostatic recurrence who received a substantial focal boost, more than 107 % of 77 Gy, to the primary GTV which was 86.5 Gy. The remaining patients, although some also assigned to the focal boost arm, all received D98% $<$ 81 Gy. In comparison, the median D98% of all patients in the focal boost arm was 84 Gy (IQR: 81–88 Gy). This reflects the concessions made to the boost dose due to the prioritization of the organs-at-risk constraints.

Discussion

We analyzed intra-prostatic recurrences in the FLAME-cohort of patients with intermediate- and high-risk prostate cancer who

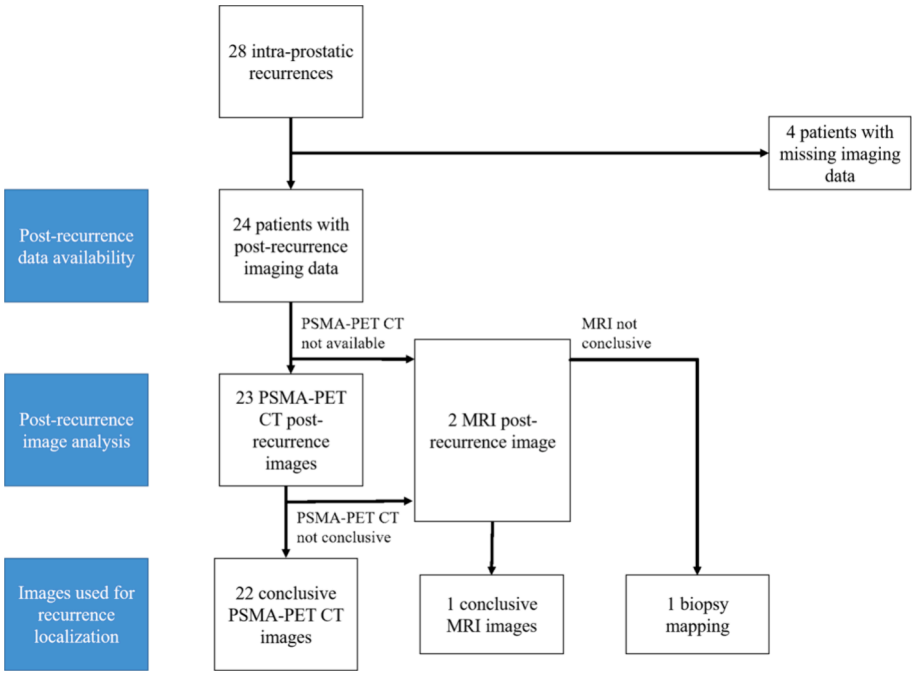

Fig. 2. Post-recurrence image availability. A flowchart displaying the post-recurrence image collection process, the availability of various imaging types and recurrence identification steps.

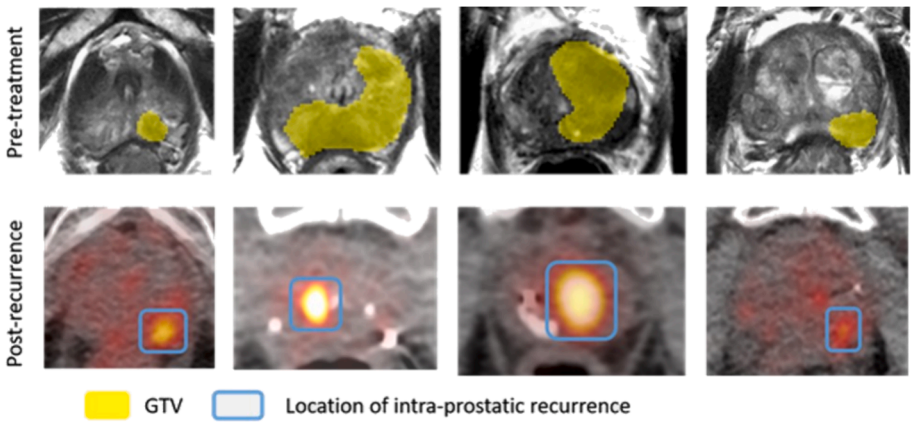

Fig. 3. Example of intra-prostatic recurrences. Top row shows examples of T2 weighted MRI with GTV delineated in yellow. Bottom row shows the corresponding registered post-recurrence PSMA-PET CT with the location of intra-prostatic recurrence highlighted in blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

underwent radiotherapy. Given the applied treatment in this cohort, we would expect that intra-prostatic recurrences might originate from outside the GTV, treated with a regular dose or from an undertreated primary tumor. The latter could be a consequence of very radio-resistant tumors that recur even when treated with high dose or cases where high focal boost dose was not reached. The image analysis showed that the intra-prostatic recurrences appeared almost always at the location of the primary GTV. This supports the hypothesis that an intra-prostatic recurrence originates from the undertreatment of primary tumor rather than from the undertreatment of the remaining prostate gland. In the pattern of failure analysis of the FLAME trial, Groen et al. reports a strong dose–response trend for local failure with the hazard ratio for focal boosting of 0.33 (0.14—0.76) [11]. Indeed, the intra-prostatic recurrences appeared mainly in patients where the dose to the GTV was not substantially escalated. This also suggests that the observed recurrences stem from residual rather than de-novo disease.

Our results support the claims of previously published research and further justify the strategy of therapy intensification at the location of the primary GTV [7,8,9,10,13]. Moreover, to maximize the efficacy of this approach, an adequate dose to the GTV has to be reached [12]. In comparison to our dosimetric findings, Mendez et al. reported unexpectedly high relapse numbers after single-fraction high dose rate brachytherapy even with a high reported D98% of 21.6 Gy at the location of recurrence [13]. As the authors suggest, this could be the consequence of the inaccuracy of the linear-quadratic model, but could also be the result of inaccurate alpha–beta estimate which has been suggested to vary dependent on the fraction size [14]. Nonetheless, with only 21 intra-prostatic recurrences out of 271 patients in the standard arm for many patients the standard dose of 77 Gy seemed to have sufficed. Our risk modeling of the FLAME trial suggests that particularly patients with GG 4 or 5 could benefit from focal boosting [6]. Using advanced planning techniques and quality assurance in the process might help in achieving this goal [5]. Furthermore, advanced target coverage monitoring might be especially interesting for patients with

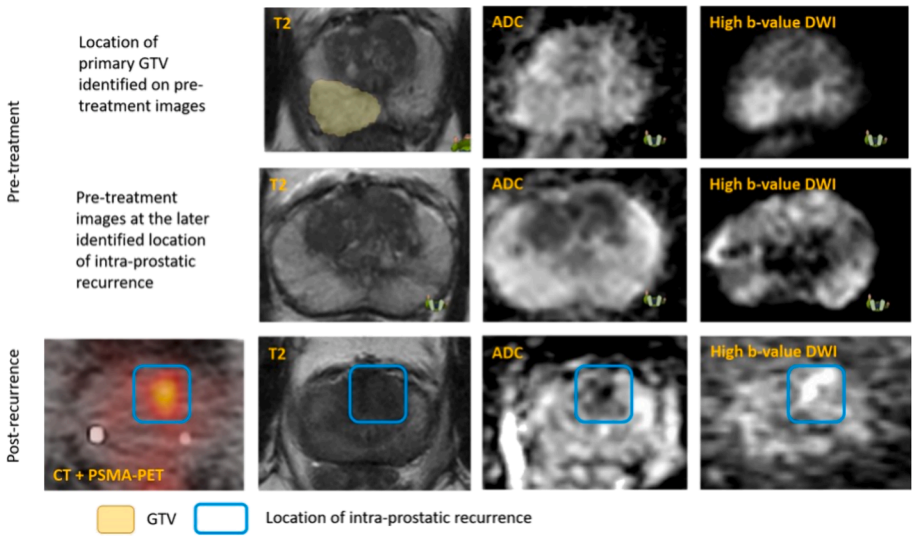

Fig. 4. Intra-prostatic recurrence at the location of anterior fibromuscular stroma. The top row shows the pre-treatment images with the location of the primary GTV of a patient who did not recur at this location. The second row shows the pre-treatment images with an intra-prostatic lesion where the recurrence was later identified. The bottom row shows the post-recurrence images, the location of the intra-prostatic recurrence is highlighted in blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

seminal vesicles involvement where possible underdosage might occur due to the extent of their motion [15].

The concept of treatment focus at the location of the primary disease is also employed by focal therapies. These therapies aim to destroy only the locations with aggressive tumor tissue using different types of energy sources, such as high-intensity focused ultrasound, cryotherapy, laser ablation and others [16]. The goal of this approach is to reduce treatment related side-effects that impact the genitourinary and gastrointestinal systems. However, there is limited evidence concerning the clinical effectiveness and the reported recurrence rates are relatively high [16,17]. This suggests that some irradiation to the remaining prostate gland is necessary to eradicate the microscopic disease in the CTV.

The historic increase in the CTV dose was originally motivated by the desire to improve the overall oncologic outcome. However, given that it is the treatment dose to the GTV that matters [3], we might reconsider the magnitude of the CTV dose. Our analysis identified only one patient with an intra-prostatic recurrence outside the GTV which was at a location of the anterior fibromuscular stroma, a location where it is difficult to recognize disease [18]. These results suggest that reduction of dose to the remaining prostate gland might be a suitable strategy for reducing treatment-related toxicity without compromising local control. Especially since intra-prostatic recurrences outside of the primary GTV already appeared to be sparse with CTV doses as low as EQD2 66 Gy ($\alpha/\beta = 1.62$) [7] when compared to the currently used standard of EQD2 77 Gy [1]. However, the level to which CTV dose could be reduced is yet to be determined, particularly in the context of hypofractionation and ultra-hypofractionation. Therefore such a strategy might be initially tested in a lower risk cohort where lower treatment dose appears to be sufficient for tumor control [19]. First trials that explore this concept can provide an estimate to what a safe CTV dose might be. An example is the DESTINATION trial (NCT05709496), a phase II trial, which currently tests the technical feasibility of a toxicity-minimizing radiotherapy treatment in the intermediate risk population. This consists of prostate gland irradiation in five fractions with a low CTV dose of 30 Gy (EQD2 63 Gy with $\alpha/\beta = 1.62$), but with a high GTV dose of 45 Gy (EQD2 132 Gy with $\alpha/\beta = 1.62$).

An adequate identification of GTV becomes crucial to the success of treatment strategies that employ therapy intensification at the location of the primary tumor. There are advancements in this area that support clinician's decision of where the disease is located. An example is the automation of tumor delineation [20], but also new imaging techniques that have been shown to reduce the inter-observer variability [21]. Also the role of PSMA-PET in disease identification was investigated by Zamboglou et al. [22]. Furthermore, targeted biopsies might provide us with a confirmation of suspicious areas identified on imaging and with information relevant to the treatment, such as the characteristics and aggressiveness of targeted lesions [23]. However, to further advance personalized planning with minimal discomfort for patients, additional research into lesion characteristics derived from imaging is warranted. As an example, Gorovets et al. found that patients with PIRADS 4 or 5 lesions are more likely to recur locally after radiotherapy with the recurrence being often located at the primary tumor site [10].

A limitation of our study is the uncertainty in the precise disease progression timeline. The imaging of patients was performed after the detection of a biochemical failure which does not always happen at the very beginning of a progression and is often recorded at a time point of a scheduled follow-up appointment. Additionally, the interobserver variability in GTV contouring based on the PSMA-PET signal also plays a role in the image analysis. Therefore, there might be some uncertainty introduced when determining the location of the intra-prostatic recurrence on the acquired images. Furthermore, the one patient where the localization of the intra-prostatic recurrence was based on pathology carried a certain level of uncertainty since the biopsy was 50 % positive. The sampled tissue which was positive could have therefore come from the surrounding rather than directly from the primary GTV location.

In conclusion, intra-prostatic recurrences after radiotherapy of intermediate and high-risk prostate cancer patients appeared predominantly at the location of the primary GTV, and mainly in patients not receiving a substantial focal boost. The fact that we observed only one CTV recurrence suggests there is room for de-escalation of dose to the remaining prostate gland.

CRediT authorship contribution statement

K. Menne Guricová: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **F.J. Pos:** Writing – review & editing, Investigation. **I.G. Schoots:** Writing – review & editing, Investigation, Data curation. **W.V. Vogel:** Writing – review & editing, Investigation, Formal analysis. **L.G.W. Kerkmeijer:** Writing – review & editing, Supervision. **E.M. Monninkhof:** Writing – review & editing. **J.C.J. de Boer:** Writing – review &

editing, Data curation. **J.R.N. van der Voort van Zyp:** Writing – review & editing, Data curation. **M. Kunze-Busch:** Writing – review & editing, Data curation. **R.J. Smeenk:** Writing – review & editing. **C. Draulans:** Writing – review & editing, Data curation. **K. Haustermans:** Writing – review & editing. **P.J. van Houdt:** Writing – review & editing, Conceptualization, Visualization, Supervision. **U.A. van der Heide:** Writing – original draft, Methodology, Conceptualization, Investigation, Supervision.

Declaration of competing interest

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

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