 doi:10.20944/preprints202205.0332.v1

Article

Toxicity of dose-escalated radiotherapy up to 84 Gray for prostate cancer

Johannes Rosenbrock[1], Christian Baues[1], Marius Kreis[1], Redouane Fouassi[1], Eren Celik[1], Pia Paffenholz[2], David Pfister[2], Axel Heidenreich[2] and Simone Marnitz[1]

[1] Department of Radiation Oncology, Cyberknife and Radiation Therapy, Faculty of Medicine and University Hospital of Cologne, University of Cologne, Kerpener St 62, 50937 Cologne, Germany
[2] Department of Urology, Faculty of Medicine and University Hospital of Cologne, University of Cologne, Kerpener St 62, 50937 Cologne, Germany

Abstract

Introduction

The outcome of radiotherapy (RT) for prostate cancer (PCA) depends on the delivered dose. While the evidence for dose-escalated RT up to 80 Gy is well established, there have been only few studies examining dose escalation above 80 Gy. We initiated the presented study to assess the safety of dose escalation up to 84 Gy.

Patients and methods

In our retrospective analysis, we included patients who received dose-escalated RT for PCA at our institution between 2016 and 2021. We evaluated acute genitourinary (GU) and gastrointestinal (GI) toxicity as well as late GU and GI toxicity.

Results

A total of 86 patients could be evaluated, of whom 24 patients had received 80 Gy and 62 patients had received 84 Gy (35 without pelvis- and 27 with pelvis-radiotherapy).

Regarding acute toxicities, no adverse events > grade 2 occurred. 12.5% of patients treated with 80Gy, in 25.7% of patients treated with 84 Gy excluding pelvis, and in 51.9% of patients treated with 84Gy including pelvis suffered from Grade 2 GU acute toxicity (80 Gy versus 84 Gy: p=0.186; with pelvis versus without pelvis: p=0.032). Grade 2 GI toxicity occurred in 12.5% of patients irradiated with 80Gy, in 14.3% of patients treated with 84 Gy excluding pelvis, and in 12.9% of patients treated with 84Gy including pelvis (80 Gy versus 84 Gy: p=0.582; with pelvis versus without pelvis: p=0.510).

GU late toxicity of grade ≥ 2 occurred in 4.2% of patients treated with 80 Gy, in 7.1% of patients treated with 84 Gy excluding pelvic RT, and in 18.2% of patients treated with 84 Gy including pelvic RT (logrank-test p=0.237). 8.3% of patients treated with 80 Gy, in 3.6% of patients treated with Gy excluding pelvic RT, and in 0% of patients treated with 84 Gy including pelvic RT suffered from GI late toxicity of grade ≥ 2(logrank-test p=0.358).

Conclusion

We were able to show that dose-escalated RT in PCA up to 84 Gy is feasible and safe without asubstantial increase in toxicity. Further follow up is needed to assess survival.

Keywords: prostate cancer; radiotherapy; toxicity; dose escalation

1. Introduction

The outcome of radiotherapy (RT) for prostate cancer (PCA) depends on the delivered dose [1 2 3 4 5 6 7 8]. Modern techniques of external beam radiation therapy (EBRT) such as intensity modulated radiation therapy (IMRT) [9] and image-guided radiation therapy (IGRT) [10] reduce the risk of side effects, allowing dose escalation compared to conventional 3D-conformal radiation therapy (3D-RT). Evidence for dose-escalated irradiation up to 78-80 Gray (Gy) is well proven for patients with a high risk PCA [11 12 13 6]. Studies

 doi:10.20944/preprints202205.0332.v1

with a brachytherapy boost suggest that further dose escalation leads to better local control [14] [15]. Spratt et al. demonstrated the efficacy and safety of EBRT with 86.2 Gy in a large retrospective study [16]. The Flame study demonstrated an advantage of an intra-prostatic EBRT-boost of up to 95 Gy over a conventional IMRT with 77 Gy [17]. However, these highly sophisticated EBRT concepts have not yet become widely accepted in clinical practice. Accordingly, European Association of Urology (EAU)/European Society for Radiotherapy and Oncology (ESTRO) guidelines recommends 74 to 80Gy for low risk PCAs and 76-78Gy for intermediate and high risk PCAs [18]. Barelkowski et al. developed a whole-gland tomotherapy up to 84 Gy using a combination of sequential and simultaneous integrated boosts (SIB). They reported excellent oncologic outcome and toxicity data in a retrospective study of 88 patients.[19] After we transferred Barelkowski's target volume- and dose-concept to volumetric modulated arc therapy (VMAT) in 2016, this concept became the new standard therapy in high risk prostate cancer patients in our institution.

The aim of the present study is to evaluate the safety of dose escalated RT up to 84 Gy in everyday clinical practice.

2. Patients and methods

In our retrospective analysis, we included all patients with a PCA who were treated in our clinic with dose escalated RT during the years 2016-2021 after informed consent. All patients gave written informed consent before the start of treatment. The patients were previously discussed in the interdisciplinary tumor board and, depending on the risk group, informed about the possible therapy options active surveilance, radical prostatectomy and radiotherapy. Depending on the risk profile, neoadjuvant and adjuvant androgen deprivation therapy (ADT) was delivered for 18 and 36 months, respectively, according to the EAU guidelines. [18]

The study was conducted in accordance with the Declaration of Helsinki in its latest version. Due to the retrospective nature, from the point of view of the local ethics committee, there is no professional consultation obligation for the North Rhine physicians according to § 15 para. 1 of the professional code of conduct.

2.1. Dose prescription and contouring

Patients with a risk of less than thirty percent for extraprostatic extension, a risk of seminal vesicle involvement less than ten percent, and a risk of lymph node involvement less than ten percent according to Memorial Sloan Kettering Center nomogram (https://www.mskcc.org/nomograms/prostate/pre-op) were usually treated with 80 Gy in two treatment steps.

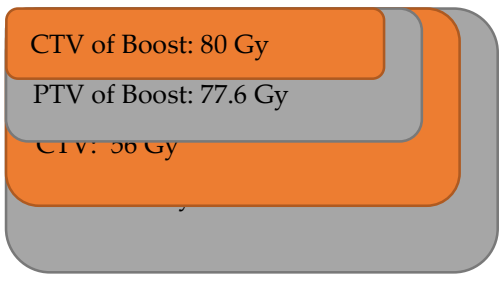

Figure 1 | Dose prescription - 80 Gy; Abbreviations: CTV, clinical target volume; PTV, planning target volume; Gy, Gray

In the first step, the clinical target volume (CTV) included the prostate and 5mm of the periprostatic space. The planning target volume (PTV) encompassed this CTV with a margin of 5 to 8 mm depending on the presence of fiducials. Dorsally, the PTV was limited to 3 to 6mmm. The PTV was radiated to 50.4 Gy with a dose of 1.8 Gy per fraction. To the CTV, a SIB was administered with a dose of 56 Gy in 2 Gy single dose. In the second

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 May 2022 doi:10.20944/preprints202205.0332.v1

treatment step (sequential boost), the CTV included only the prostate. The PTV (margins see above) was treated with 21.6 Gy of irradiation in 1.8 Gy per fraction in the second step. A SIB of 24 Gy in 2 Gy single dose was administered to the CTV of the sequential boost. Cumulatively, this results in 80 Gy (56 Gy +24 Gy). Figure 1 shows the dose prescription of the patients treated with 80Gy.

Alternatively, patients with low risk PCA could be irradiated with standard radiotherapy, i.e. continuously up to 80 Gy in 2 Gy single dose. The prostate was defined as CTV and the PTV was placed with a margin of 5mmm (dorsally 3 mmm) around the CTV. In this case, neither a simultaneous nor a sequential boost was administered.

Patients with a risk greater than thirty percent for extraprostatic extension or a risk of seminal vesicle involvement greater than ten percent and at the same time a risk of lymph node involvement less than ten percent according to Memorial Sloan Kettering Center nomogram were usually treated with 84 Gy in two treatment steps.

Figure 2 | Dose prescription - 84 Gy prostate only; Abbreviations: CTV, clinical target volume; PTV, planning target volume; Gy, Gray

In the first step, the CTV included the prostate, the periprostatic space up to the pelvic wall, and the proximal two centimeters of the seminal vesicles. The PTV (margins see above) was radiated to 59.4 Gy with a dose of 1.8 Gy per fraction. To the CTV, a SIB was administered with a dose of 66 Gy in 2 Gy single doses. In the second treatment step (sequential boost), the CTV included only the prostate. The PTV (margins see above) was treated with 16.2 Gy in 1.8 Gy per fraction in the second step. A SIB of 18 Gy in 2 Gy single dose was administered to the CTV of this sequential boost. Cumulatively, this results in 84 Gy (66 Gy +18 Gy). Figure 2 shows the dose prescription of the patients treated with 84Gy prostate only.

Current guidelines[18] are cautious in recommending prophylactic pelvic irradiation due to unclear data[20]. Nevertheless, many studies, that established the combination therapy consisting of radiotherapy and ADT, included pelvic irradiation [21 22 23]. Therefore we discussed pelvic irradiation individually with patients who had a risk of lymph node involvement greater than ten percent and especially greater than fifteen percent.

If pelvic irradiation was performed, it consisted of three therapy steps. In the first step, the CTV included the prostate, the periprostatic space up to the pelvic wall, the proximal two centimeters of the seminal vesicles and the pelvic lymph nodes up to the level of the junction of L5 and S1. The PTV encompassed this CTV with a margin of 8 mm and was radiated to 45 Gy with a dose of 1.8 Gy per fraction. To the CTV, a SIB was administered with a dose of 50 Gy in 2 Gy single doses. In the second treatment step (first sequential boost), the CTV included the prostate, 5mm of the periprostatic space, and the proximal two centimeters of the seminal vesicles. The PTV (5-8 mm margin, dorsally 3-6 mm) was treated with 19.8 Gy in 1.8 Gy per fraction. A SIB of 22 Gy in 2 Gy single dose was administered to the CTV of the first sequential boost. The CTV of the second sequential boost includes only the prostate. The PTV (5-8 mm margin, dorsally 3-6 mm) was radiated with 10.8 Gy per fraction. A SIB of 12 Gy in 2 Gy single dose was administered to the CTV

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 May 2022 doi:10.20944/preprints202205.0332.v1

of the second sequential boost. Cumulatively, this results in 84 Gy (50 Gy + 22 Gy +12 Gy). Figure 3 shows the dose prescription of the patients treated with 84Gy whole pelvis andTable 1 summarizes the whole radiotherapy concept.

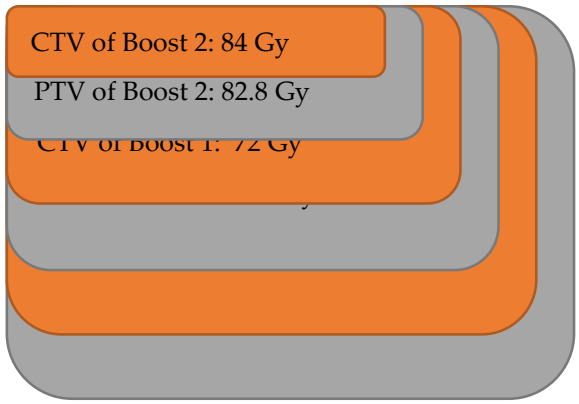

Figure 3 | Dose prescription - 84 Gy whole pelvis; Abbreviations: CTV, clinical target volume; PTV, planning target volume; Gy, Gray

	80 Gy		84 Gy without pelvis		84 Gy with pelvis	
Therapy step 1	CTV1: prostate and 5mm of the PS		CTV1: prostate, the PS up to the pelvic wall, and SV		CTV1: prostate, the PS up to the pelvic wall, SV and the pelvic LN	
	PTV1	SIB to CTV1	PTV1	SIB to CTV1	PTV1	SIB to CTV1
Dose	50.4 Gy	56 Gy	59.4 Gy	66Gy	45Gy	50Gy
Number of fractions	28	28	33	33	25	25
Therapy step 2	CTV2: prostate		CTV2: prostate		CTV2: prostate, 5mm of the PS, and SV	
	PTV2	SIB to CTV2	PTV2	SIB to CTV2	PTV2	SIB to CTV2
Dose	21.6 Gy	24 Gy	16.2 Gy	18 Gy	19.8 Gy	22 Gy
Number of fractions	12	12	9	9	11	11
Therapy step 3					CTV3: prostate	
					PTV3	SIB to CTV3
Dose					10.8 Gy	12 Gy
Number of fractions					6	6
Dose sum		80Gy		84 Gy		84Gy

Table 1: Radiotherapy concept; Abbreviations: CTV, clinical target volume; PTV, planning target volume; Gy, Gray; PS, periprostatic space; SV, proximal two centimeters of the seminal vesicles; LN lymph nodes

2.2. Radiotherapy planning

The plans used in this study are in RapidArc (two to four arcs) and helical tomotherapy IMRT (Field width 2.5 cm) technology. They were created using the Eclipse planning system (Varian Medical Systems Inc., version 13.6) and Precision planning system (Accuray Precision, version 2.0.1.1).

The dose calculation for Eclipse was performed with the anisotropic analysis algorithm (AAA, version 13.6.23) and for Precision planning system was the Convolution-Superposition.

 doi:10.20944/preprints202205.0332.v1

The required volume coverage was 95% of the PTV's should be covered with at least 97% of the prescription dose.

2.3. Statistics

We evaluated progression-free survival (PFS), local recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS). Moreover, we investigated the acute and late genitourinary (GU) and gastrointestinal (GI) toxicity.

PFS, LRFS and DMFS were calculated using the Kaplan-Meier method. For PFS, events included death, progression, recurrence (according to Phoenix criteria or by histologic confirmation), and occurrence of metastases. Regarding LRFS, the events were recurrence according to the Phoenix criteria or by histological confirmation. Patients irradiated with 80 Gy or with 84 Gy were considered separately. We did not compare the treatment groups for survival data by log-rank test because the risk profiles of the groups differed substantially.

We classified adverse events that occurred within 90 days of RT start initiation as acute toxicity and used Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) to evaluate acute toxicity. Acute toxicities grade ≥ 2 were assessed between the three different treatment regimens (80 Gy, 84Gy without pelvis, 84Gy with pelvis) using Fisher's exact test.

Late toxicity was defined as adverse events that persisted or occurred after 90 days following initiation of RT. We used the LENT SOMA system[24] to assess late toxicities. Patients with a follow up smaller than 90 days after RT start were excluded from the late toxicity assessment. Late grade ≥ 2 toxicities were evaluated using a log-rank test between the three different treatment regimens (80 Gy, 84Gy without pelvis, 84Gy with pelvis).

We performed the statistical analysis using IBM SPSS Statistica Version 28.0.1.0.

3. Results

3.1. Patients

A total of 86 patients could be evaluated, of whom 24 patients had received 80 Gy and 62 patients had received 84 Gy (35 without pelvis- and 27 with pelvis-radiotherapy). The mean follow-up time for the survival data was 13.2 months (minimum 0 months, maximum 60 months). Because patents with an FU less than 3 months were excluded for the long-term toxicity analysis, the mean follow-up time here was 15.2 months (minimum 3 months, maximum 60 months). Table 2 shows the patient characteristics.

		80 Gy		84 Gy prostate only		84 Gy with whole pelvis		84 Gy total	
Tumor stage		n	%	n	%	n	%	n	%
	1a	1	4.2	0	0.00	0	0.00	0	0
	1b	0	0	0	0.00	0	0.00	0	0
	1c	20	83.3	21	60.00	13	48.10	34	54.8
	2a	2	8.3	3	8.57	2	7.40	5	8.1
	2b	0	0	1	2.86	4	14.80	5	8.1
	2c	1	4.2	9	25.71	5	18.50	14	22.6
	3a	0	0	0	0.00	1	2.70	1	1.6
	3b	0	0	1	2.86	2	7.40	3	4.8
Gleason score		n	%	n	%	n	%	n	%
	6	15	62.5	5	14.29	0	0.00	5	8.1
	7a	8	33.3	17	48.57	3	11.10	20	32.3
	7b	1	4.2	3	8.57	4	14.80	7	11.3

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 May 2022 doi:10.20944/preprints202205.0332.v1

	8	0	0	8	22.86	13	48.10	21	33.9
	9	0	0	2	5.71	7	25.90	9	14.5
iPSA		mean	SD	mean	SD	mean	SD	mean	SD
		8.11	4.30	12.24	17.46	39.13	111.00	23.95	74.84
D'Amico risk group		n	%	n	%	n	%	n	%
	low	13	54.2	1	2.86	0	0.00	1	1.6
	intermediate	9	37.5	19	54.29	1	3.70	20	32.3
	high	2	8.3	15	42.86	26	96.30	41	66.1
ADT use	yes	3	12.5	15	42.90	26	96.30	41	66.1
	no	21	87.5	20	57.10	1	3.70	21	33.9

Table 2: patient characteristics; Abbreviations: Gy, Gray; iPSA, initial prostate specific antigen; ADT, androgen deprivation therapy; SD, standard deviation

3.2. Progression-free survival

With regard to PFS, 86 patients were evaluated, of whom 24 patients received 80 Gy and 62 patients received 84 Gy (35 without pelvis- and 27 with pelvis-radiotherapy). Among patients treated with 80 Gy, three events occurred, whereas among patients treated with 84 Gy, only one event occurred. Local recurrence occurred in one patient treated with 80 Gy. None of the patients treated with 84 Gy developed a local recurrence. Two patients, of whom one was treated with 80 Gy and one with 84 Gy, developed bone metastases during follow-up. The metastases of the patient treated with 80 Gy were not confirmed histologically and were more likely due to a renal cell carcinoma that was also detected. However, the occurrence of the metastases were nevertheless considered as an event. One patient treated with 80 Gy died because of reasons unrelated to PCA and the therapy of PCA. Figure 4 shows PFS.

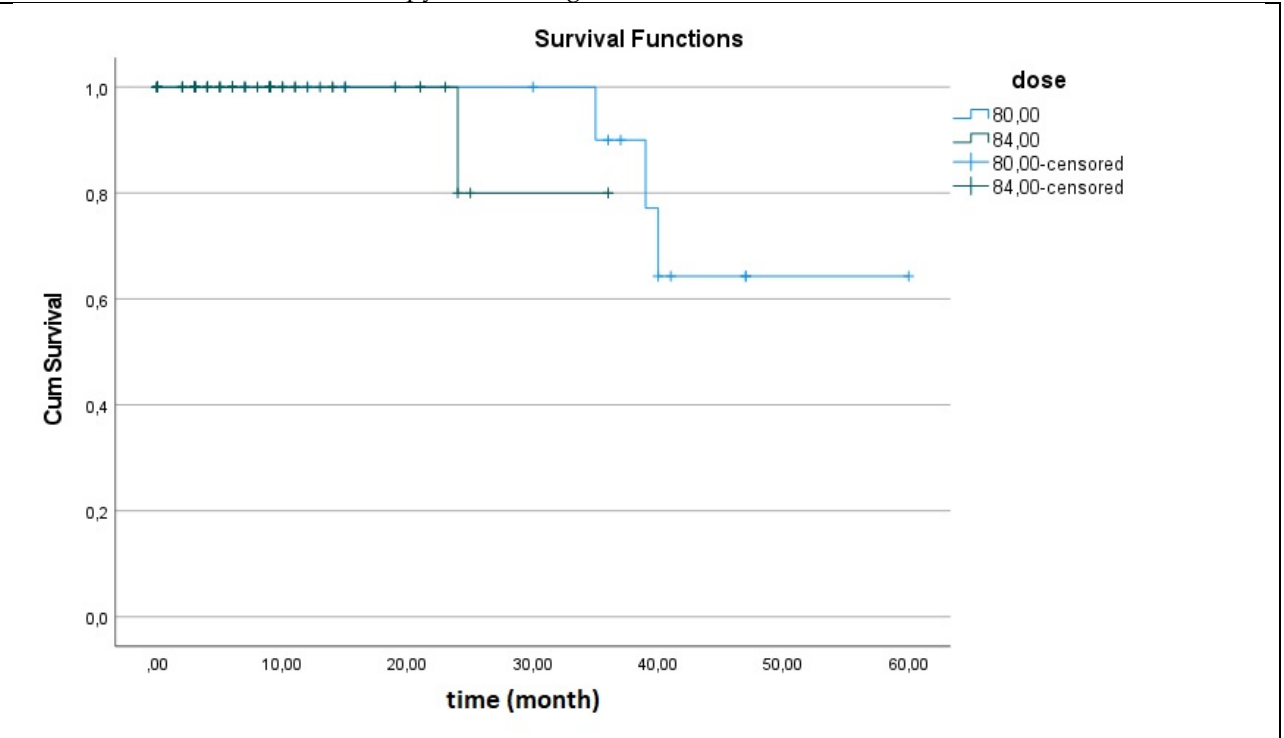

Figure 4 | Progression-free survival of patients treated with 80 Gy and 84 Gy

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 May 2022 doi:10.20944/preprints202205.0332.v1

3.3. Local recurrence-free survival

With regard to LRFS, 86 patients were evaluated, of whom 24 patients received 80 Gy and 62 patients received 84 Gy (35 without pelvis- and 27 with pelvis-radiotherapy). Local recurrence did not occurred in any of the patients treated with 84 Gy, whereas one patient with an intermediate risk PCA treated with 80 Gy developed local relapse. Remarkably, the patient who developed the local recurrence had been treated with standard radiotherapy without simultaneous boost. Figure 5 shows the Kaplan-Meier curve of LRFS of the patients treated with 80 Gy.

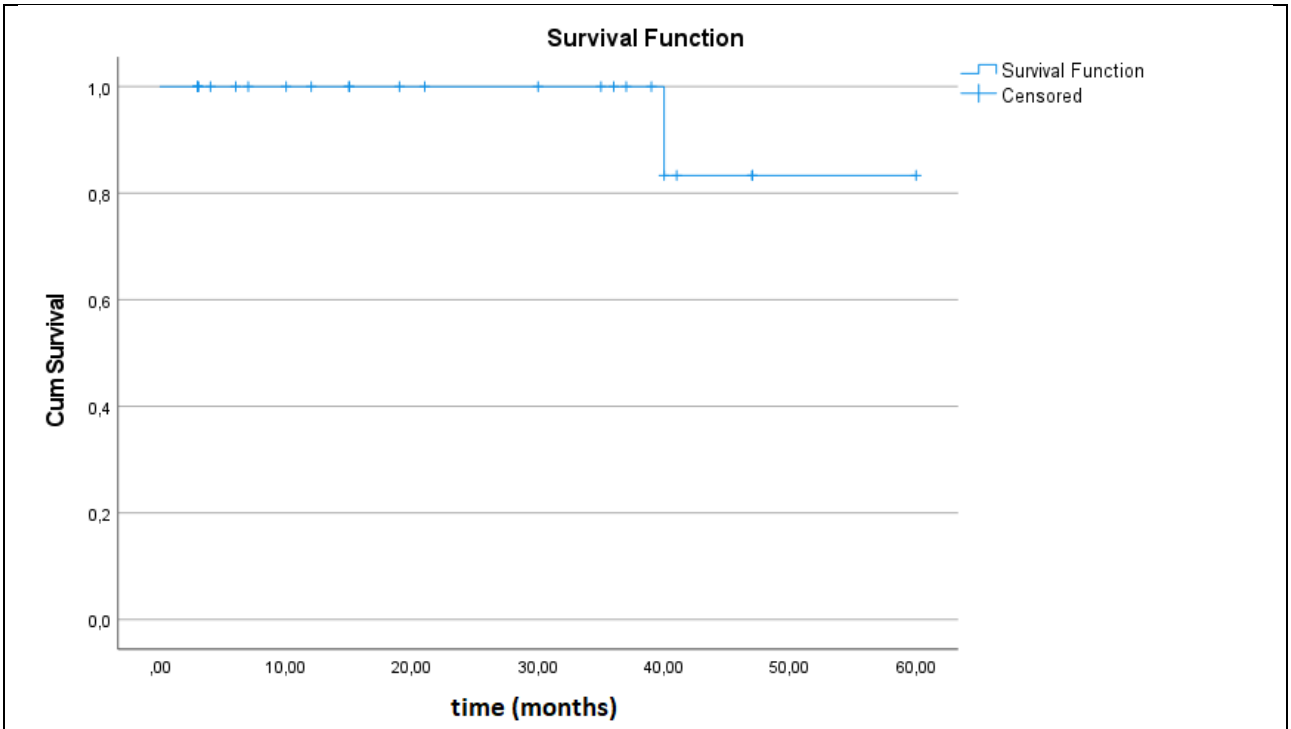

Figure 5 | Local recurrence-free survival of patients treated with 80 Gy

3.4. Distant metastasis-free survival

With regard to DMFS, 86 patients were evaluated, of whom 24 patients received 80 Gy and 62 patients received 84 Gy (35 without pelvis- and 27 with pelvis-radiotherapy). One patient treated with 80 Gy developed bone metastases in the follow-up, as did one patient treated with 84 Gy including pelvic irradiation. None of the patients treated with 84 Gy excluding pelvic irradiation developed distant metastases. The metastases of the patient treated with 80 Gy were not confirmed histologically and were probably due to renal cell carcinoma, which was also found. Nevertheless, the bone metastases were considered as an event. Figure 6 show DMFS.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 May 2022 doi:10.20944/preprints202205.0332.v1

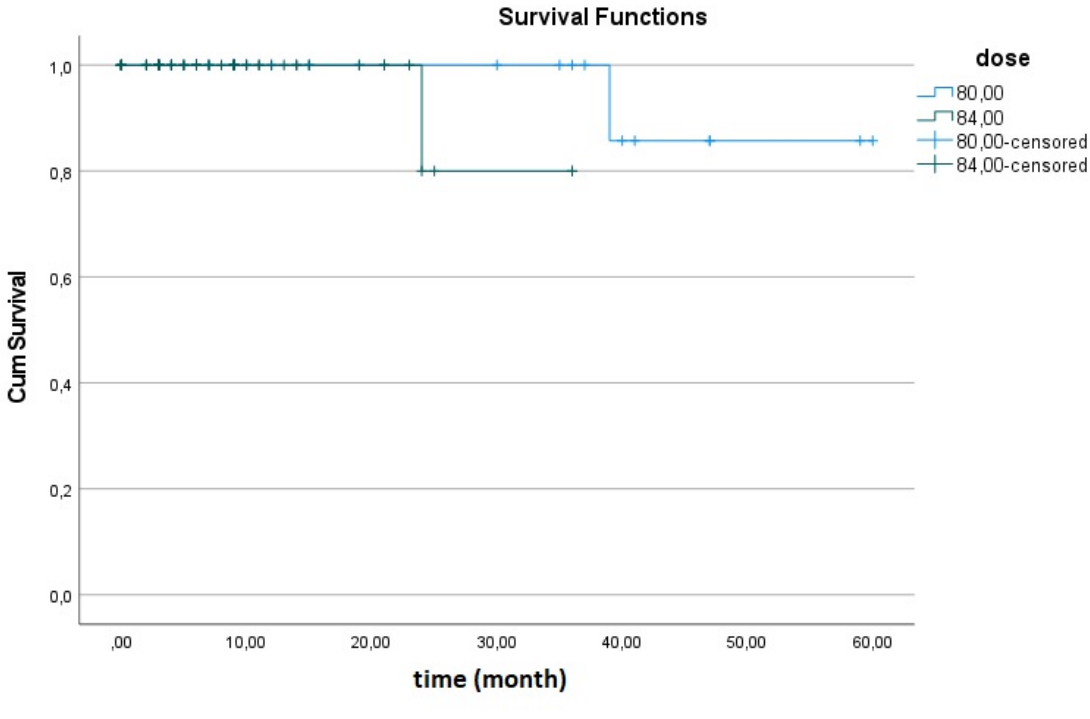

Figure 6 | Distant metastasis-free survival of patients treated with 80 Gy and 84 Gy

3.5. Acute toxicity

Regarding acute toxicity, 86 patients were analyzed, of whom 24 patients had received 80 Gy and 62 patients had received 84 Gy (35 without pelvis- and 27 with pelvis-radiotherapy).

Regarding grade ≥ 2 GU toxicity, there is no significant difference in Fisher's exact test (p=0.186) when comparing patients treated to 80 Gy with patients treated to 84Gy excluding the pelvis. In contrast, patients treated with 84Gy including pelvic RT were significantly more likely to have grade ≥ 2 GU toxicity than patients treated with 84Gy without pelvic RT (p=0.032). Table 3 shows acute GU toxicity.

	80 Gy		84 Gy without pelvis		84 Gy with pelvis		84 Gy total	
CTCAE grade	n	%	N	%	n	%	n	%
0	10	41.70	10	28.57	8	29.6	18	29.00
1	11	45.80	16	45.71	5	18.5	21	33.90
2	3	12.50	9	25.72	14	51.9	23	37.10
3	0	0.00	0	0.00	0	0.00	0	0.00
4	0	0.00	0	0.00	0	0.00	0	0.00
5	0	0.00	0	0.00	0	0.00	0	0.00

Table 3: Acute genitourinary toxicity

Regarding grade ≥ 2 GI toxicity, Fisher's exact test showed no significant difference (p=0.582) when comparing patients treated with 80 Gy to patients treated with 84 Gy excluding the pelvis. Also, there was no significant difference in grade ≥ 2 GI toxicity in patients treated with 84Gy between those with and without pelvic irradiation (p=0.510). Table 4 shows acute GI toxicity.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 May 2022 doi:10.20944/preprints202205.0332.v1

	80 Gy		84 Gy without pelvis		84 Gy with pelvis		84 Gy total	
CTCAE grade	n	%	n	%	n	%	n	%
0	17	70.80	18	51.43	18	66.7	36	58.10
1	4	16.70	12	34.29	6	22.2	18	29.00
2	3	12.50	5	14.29	3	11.1	8	12.90
3	0	0.00	0	0.00	0	0.00	0	0.00
4	0	0.00	0	0.00	0	0.00	0	0.00
5	0	0.00	0	0.00	0	0.00	0	0.00

Table 4: Acute gastrointestinal toxicity

3.6. Late toxicity

Regarding late toxicity, we were able to evaluate 74 patients after exclusion of patients with missing data or without sufficient FU. Twenty-four of these patients were irradiated with 80 Gy and 50 patients (28 without pelvis, 22 with pelvis) were irradiated with 84 Gy.

4.17% of patients treated with 80 Gy, 7.14% of patients treated with 84Gy excluding pelvis RT, and 18.18% of patients treated with 84Gy including pelvis had grade ≥ 2 GU late toxicity. There was no significant difference in logrank-test (p=0.237). Figure 7 shows GU late toxicity.

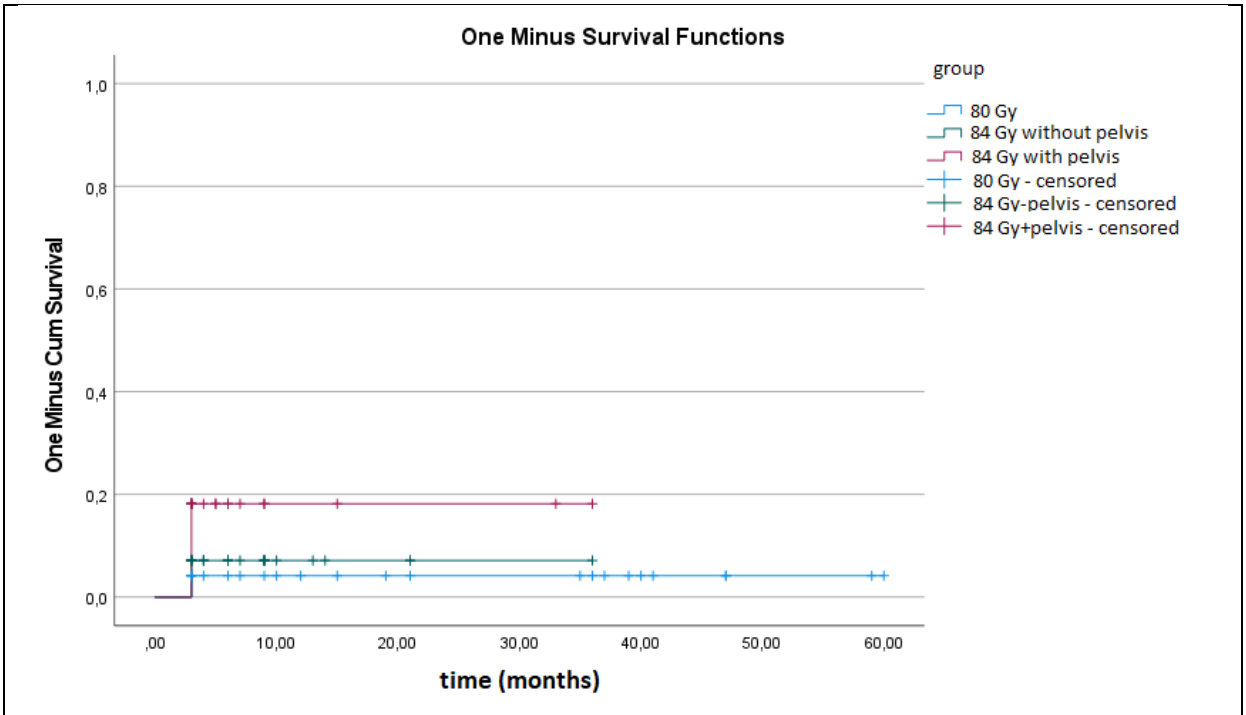

Figure 7 | Late grade two or higher genitourinary toxicity

8,33% of patients treated with 80 Gy, 3,57% of patients treated with 84Gy excluding pelvis RT, and und 0% of patients treated with 84Gy including pelvis had grade ≥ 2 GI

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 May 2022 doi:10.20944/preprints202205.0332.v1

late toxicity. There was no significant difference in logrank-test (p=0.358). Figure 8 shows GI late toxicity.

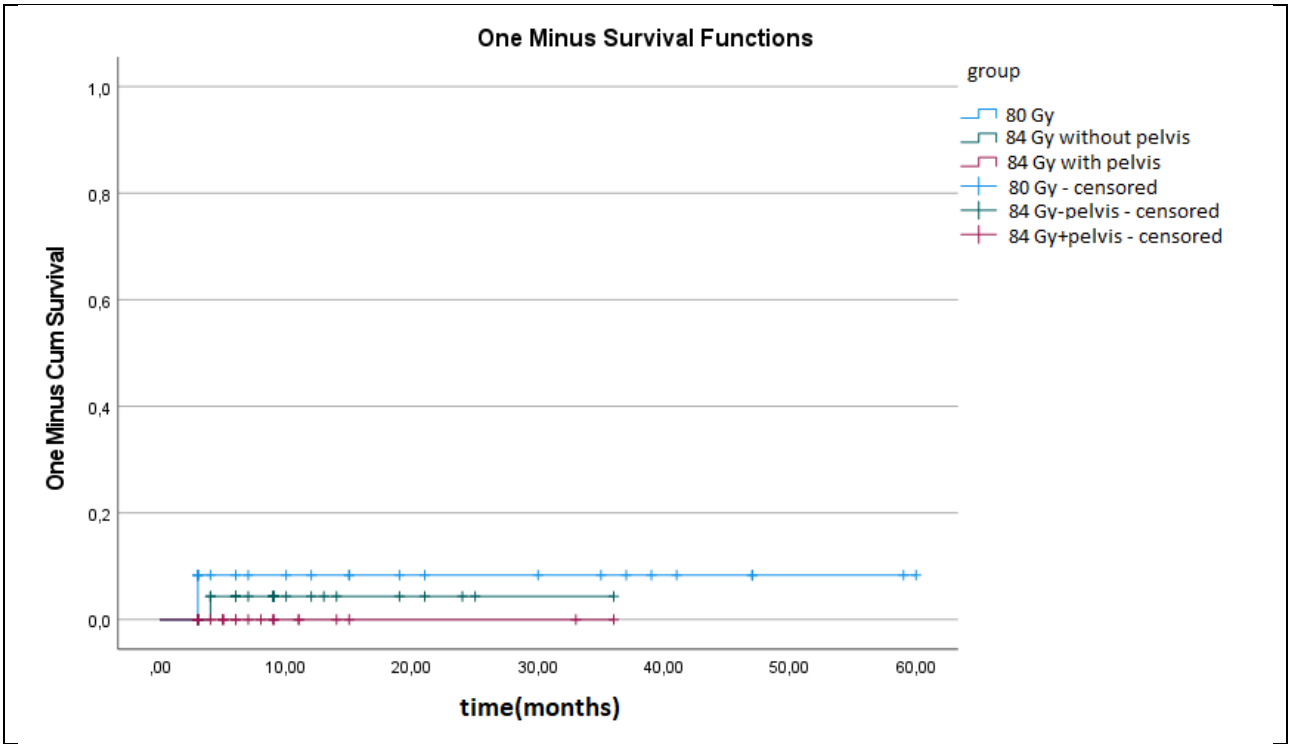

Figure 8 | Late grade two or higher gastrointestinal toxicity

4. Discussion

We have learned from various studies that the applied dose for radiotherapy of PCA has a crucial influence on the local control [1 2 3 4 5 6 7 8]. Modern irradiation techniques such as IMRT[9] and IGRT[10] allow dose escalation without major expansion of the toxicity. Barelkowski et al. [19] and Spratt et al.[16] have published solid data for 84 and 86 Gy, respectively. However, these doses have not yet been established in clinical practice. Therefore, further evidence seems to be necessary.

Our analysis was designed to investigate the safety of dose-escalated therapy. Due to the relatively short median follow-up time, we are not yet in a position to make truly adequate statements on survival. Nevertheless, for being complete, we also present the survival data. It is remarkable that in patients treated with 80Gy - i.e. primarily low and intermediate risk patients - the PFS drops below 70% after 30 months. However, due to the shorter follow-up time and small number of cases, only three patients cause this. In one patient treated with 80 Gy, bone metastases occurred during follow-up, but these were more likely from concurrent renal cell carcinoma. Another patient died of reasons unrelated to PCA or PCA therapy. One patient had a local recurrence. Therefore, there was only one event that was related to the tumor disease or the therapy. This relativizes the poor PFS data. It is also interesting that the local recurrence occurred in a patient who was conventionally irradiated with 80 Gy, i.e. not with the SIB concept presented in Table 1. In patients irradiated with 84 Gy, no local recurrence occurred and only one patient developed metastases during follow-up. Since 66% of the patients treated with 84Gy and even 96% of the patients treated with whole pelvis received a combination therapy of RT and ADT, it is not unexpected that no local recurrence occurred in the short FU time. Again, due to the shorter follow-up time, the single patient with metastases has a strong impact on the PFS curve. Nevertheless, with a PFS of 80% for intermediate and high-risk

 doi:10.20944/preprints202205.0332.v1

patients, our data are comparable to those of Barelkowski (biochemical relapse-free survival 92.8% and 70.4% for intermediate and high-risk patients)[19] and Spratt (biochemical relapse-free survival 85.6% and 67.9% for intermediate and high-risk patients)[16]. Nevertheless, further follow-up would be necessary to make reliable statements on survival.

Acute GU-toxicities in our patient cohort can be compared with those described in the literature. Barelkowski reports 19.3% grade 0, 39.8% grade 1, 39.8% grade 2, and 1.1% grade 3 acute GU toxicity for his collective[19]. This collective includes patients treated with 80 Gy or 84 Gy with and without pelvic irradiation. In our patients no acute grade 3 GU toxicity occurred. The grade 2 toxicities for the patients treated with 80Gy and for the patients treated with 84Gy excluding pelvic RT are below the values of Barelkowski. Only the patients with pelvic irradiation had more acute grade 2 toxicities than Barelkowski`s cohort (51,9% versus 39,8%). However, in Barelkowski`s collective pelvic RT was performed in only 12.5% of cases[19]. There was also no increased acute GU toxicity compared with data from randomized trials for dose escalation up to 80 Gy [3 6 25]. In our series, we could detect a significant difference between RT with pelvis and RT without pelvis, but no difference between 80Gy and 84Gy. Therefore, it can be concluded that pelvic irradiation probably leads to more acute GU toxicities than dose escalation to 84 Gy.

Regarding acute GI toxicity, the results were also similar to those of Barelkowski, who reported grade 1 and 2 GI toxicities in 29% and in 11% of his patients, respectively[19]. In our patients treated with 84 Gy, grade 1 and 2 GI toxicities occurred in 29% and 12.9%. Patients treated with 80 Gy had lower GI toxicity (Grade 1: 16.7%; Grade 2:12.5%). Grade 3 or higher GI toxicities did not occur neither in Barelkowski's study nor in our study. In the randomized "80Gy"-studies by Beckendorf et al. [6] and Peeters et al. [25], acute GI toxicities were considerably higher than in our series; in particular, grade 3 toxicities also occurred (range 4%-5.9%). This is probably due to the 3D-RT primarily used in these studies. Overall, we were able to achieve reduced GI toxicity due to the modern RT technique despite further dose escalation to 84 Gy. This is also true with regard to the proton boost study by Zietmann et al. in which no grade 3 GI toxicities occurred, but still considerably more grade 2 toxicities occurred (57%) [3].

Our data show a very favorable late GU toxicity profile compared to the data published in the literature. In our analysis, 4.2% of patients treated with 80 Gy and 7.1% of patients treated with 84 Gy without pelvis, had grade ≥ 2 GU late toxicity. 18.8% of the patients who received pelvic radiotherapy, had grade ≥ 2 GU late toxicity. In comparison, Barelkowski et al. reported a rate of 23.8% of grade ≥ 2 GU late toxicity in a pooled analysis of patients treated with 80 Gy and 84 Gy [19]. Spratt reported a rate of 21.1% [16]. Also, compared to the grade ≥ 2 late GU toxicity rate of the randomized dose escalation studies up to 80 Gy (range 21% - 26.9%) [3 6 25], the observed toxicity appears to be quite low. Comparable to our late GU toxicity is the rate of 4% reported by Pahlajani et al. for patients treated with ≥ 80Gy [7]. Our low GU late toxicity is certainly caused by the shorter follow-up compared to the other studies. We can see from Spratt's data that late toxicity increases continuously in the first 10 years [16], so that our follow-up time (mean: 15.2 months) is clearly too short to make a final assessment of late toxicity. Nevertheless, one has to consider that also our patients treated with a pelvic radiotherapy had less toxicity than the patients did the other described data. This is despite the fact that in these studies no pelvic irradiation was performed, or in Barelkowski's collective only in 12.5% of patients. Spratt et al. were able to show that acute toxicities have a high predictive value with regard to late toxicity [16]. Due to our low acute toxicity, we can therefore assume that our toxicity rate will increase in the further follow up, but not severely in comparison with the other studies. This assumption is supported by the fact that our data do not show an increase during the follow-up. Overall, our cohort shows a very favorable GU late adverse event rate.

In addition, the late GI toxicity rate of our patients is low compared to the rate of other dose-escalated trials. In our cohort, the rate of grade ≥ 2 GI toxicity was 3.6% for the patients treated with 84 Gy excluding pelvis and 0% for the patients treated with pelvis. In contrast, however, the patients treated with 80 Gy showed higher GI toxicity with a

proportion of 8.3%. Barelkowski et al. reported a proportion of 15.8% for grade ≥ 2 GI toxicity in his pooled patient collective [19]. In the trial of Spratt et al., 4.4% of patients had grade 2 or GI late toxicity [16] and in the study of Pahlajani et al. 7% of the patients treated with ≥ 80Gy [7]. Also, compared to the studies that provide the rationale for dose escalation up to 80 Gy (range for grade ≥ 2 GI toxicity: 18% - 41.7% [3 6 25]), our data suggest a low GI toxicity . Again, the short follow-up is certainly partly responsible for the low toxicity rate compared with the other trials. However, Spratt et al also demonstrated a strong association with acute GI toxicity for late GI toxicity [16]. Since our acute GI toxicity is low, especially in comparison to Beckendorf et al. [6], Peeters et al. [25] and Zietmann et al [3], one can assume that the expected increase in late toxicity will not be drastic. This would be explained by the modern irradiation technique compared to 3D-RT. Altogether, dose escalated therapy up to 84 Gy is well tolerated with respect to GI late toxicity.

Another method of dose escalation is the combination of EBRT and HDR brachytherapy. Hoskin et al. were able to show that this combination is significantly superior to hypofractionated non-dose-escalated EBRT in terms of recurrence-free survival. There was no difference with regard to long-term toxicity [26]. However, the EBRT regimen with 55 Gy in 20 fractions corresponds only to an EQD2 of 65.9 Gy, based on an α/β ratio of 1.8 Gy. In this respect, the standard arm cannot be compared with the dose-escalated normofractionated RT-regimens discussed here (EQD2 ≥ 80 Gy) as well as with the in between established standard in moderate hypofractionation (CHHip-trial, 60 Gy in 20 fraction [27]; EQD2 of 75.9 Gy). Morris et al. demonstrated a significant advantage of a combination of EBRT (46 Gy in 23 fractions and LDR brachytherapy (minimal peripheral dose of 115 Gy) over EBRT alone (78 Gy in 29 fractions) in terms of biochemical progression-free survival [14], but more grade 3 GU late adverse events occurred after the combination (18.4% versus 5.2% P<.001) [28].

To our knowledge, a randomized trial evaluating combination therapy including brachytherapy versus dose-escalated RT > 80 Gy does not exist. However, Spratt et al. were able to demonstrate an advantage of a combination of EBRT and brachytherapy over dose-escalated EBRT (86.4 Gy) in terms of recurrence-free survival in a retrospective series. Higher acute GU toxicity occurred with combination therapy, but no higher rate of long-term toxicities. According to the authors, many patients were irradiated using IGRT without fiducial markers, which may have influenced the accuracy of EBRT [15]. Overall, this study clearly demonstrate the potential of dose-escalated RT using brachytherapy. Nevertheless, there is a lack of randomized trials demonstrating superiority of combining brachytherapy with EBRT compared with >80Gy dose-escalated EBRT.

As an alternative to the whole-gland dose escalated RT applied in our study, dose escalation by intraprostatic boost is an option. The Flame study achieved a 5-year biochemical disease-free survival of 92% in a population of mainly high-risk patients. Regarding late GU and GI toxicity, there was only a trend to more toxicity without significance compared to the standard 77Gy treatment arm (GU toxicity grade ≥ 2: 28% versus 23%; GI toxicity grade ≥ 2: 13% versus 12%) [17].Nevertheless, the concept of intraprostatic EBRT boost still needs to be established in clinical practice. The authors themselves critically address the interobserver variability in the contouring of the GTV, although the study shows excellent results despite this interobserver variability. However, it is unclear whether this has a critical effect outside of a clinical study.

5. Conclusion

Intraprostatic EBRT-boost will certainly be used more frequently in the future and brachytherapy shows promising results. Nevertheless, whole-gland EBRT, which has been successfully used over decades, will continue to play a significant role in everyday clinical practice. Our data show that dose escalation above 80 Gy with appropriate techniques like IMRT and daily IGRT is possible and safe. Further follow up is needed to assess survival.

 doi:10.20944/preprints202205.0332.v1

References:

1. Hanks GE, Martz KL, Diamond JJ: The effect of dose on local control of prostate cancer. International Journal of Radiation Oncology*Biology*Physics 15:1299–1305, 1988
2. Kuban DA, Tucker SL, Dong L, et al: Long-Term Results of the M. D. Anderson Randomized Dose-Escalation Trial for Prostate Cancer. International Journal of Radiation Oncology*Biology*Physics 70:67–74, 2008
3. Zietman AL, DeSilvio ML, Slater JD, et al: Comparison of Conventional-Dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the ProstateA Randomized Controlled Trial. JAMA 294:1233–1239, 2005
4. Peeters STH, Heemsbergen WD, Koper PCM, 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. JCO 24:1990–1996, 2006
5. Dearnaley DP, Sydes MR, Graham JD, et al: Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. The Lancet Oncology 8:475–487, 2007
6. Beckendorf V, Guerif S, Le Prisé E, et al: 70 Gy Versus 80 Gy in Localized Prostate Cancer: 5-Year Results of GETUG 06 Randomized Trial. International Journal of Radiation Oncology*Biology*Physics 80:1056–1063, 2011
7. Pahlajani N, Ruth KJ, Buyyounouski MK, et al: Radiotherapy Doses Of 80 Gy And Higher Are Associated with Lower Mortality in Men With Gleason Score 8 to 10 Prostate Cancer. Int J Radiat Oncol Biol Phys 82:10.1016/j.ijrobp.2011.04.005, 2012
8. Eade TN, Hanlon AL, Horwitz EM, et al: WHAT DOSE OF EXTERNAL-BEAM RADIATION IS HIGH ENOUGH FOR PROSTATE CANCER? Int J Radiat Oncol Biol Phys 68:682–689, 2007
9. Yu T, Zhang Q, Zheng T, et al: The Effectiveness of Intensity Modulated Radiation Therapy versus Three-Dimensional Radiation Therapy in Prostate Cancer: A Meta-Analysis of the Literatures. PLoS One 11:e0154499, 2016
10. Zelefsky MJ, Kollmeier M, Cox B, et al: Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 84:125–129, 2012
11. Pollack A, Zagars GK, Starkschall G, et al: Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys 53:1097–1105, 2002
12. Zietman AL, Bae K, Slater JD, et al: Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol 28:1106–1111, 2010
13. Heemsbergen WD, Al-Mamgani A, Slot A, et al: Long-term results of the Dutch randomized prostate cancer trial: Impact of dose-escalation on local, biochemical, clinical failure, and survival. Radiotherapy and Oncology 110:104–109, 2014
14. Morris WJ, Tyldesley S, Rodda S, et al: Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer. International Journal of Radiation Oncology*Biology*Physics 98:275–285, 2017
15. Spratt DE, Zumsteg ZS, Ghadjar P, et al: Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer. BJU International 114:360–367, 2014
16. Spratt DE, Pei X, Yamada J, et al: Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 85:686–692, 2013
17. Kerkmeijer LGW, Groen VH, Pos FJ, et al: 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 39:787–796, 2021
18. EAU Guidelines Office: EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2022. Arnhem, The Netherlands, EAU Guidelines Office
19. Barelkowski T, Wust P, Kaul D, et al: Image-guided dose-escalated radiation therapy for localized prostate cancer with helical tomotherapy. Strahlenther Onkol 196:229–242, 2020
20. Roach M, Moughan J, Lawton CAF, et al: Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): long-term results of a randomised, phase 3 trial. Lancet Oncol 19:1504–1515, 2018
21. Bolla M, Van Tienhoven G, Warde P, et al: External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 11:1066–1073, 2010
22. Lawton CAF, Lin X, Hanks GE, et al: Duration of Androgen Deprivation in Locally Advanced Prostate Cancer: Long-Term Update of NRG Oncology RTOG 9202. Int J Radiat Oncol Biol Phys 98:296–303, 2017
23. Nabid A, Carrier N, Martin A-G, et al: Duration of Androgen Deprivation Therapy in High-risk Prostate Cancer: A Randomized Phase III Trial. Eur Urol 74:432–441, 2018
24. Lent soma scales for all anatomic sites. International Journal of Radiation Oncology*Biology*Physics 31:1049–1091, 1995

 doi:10.20944/preprints202205.0332.v1

25. Peeters STH, Heemsbergen WD, van Putten WLJ, et al: Acute and late complications after radiotherapy for prostate cancer: Results of a multicenter randomized trial comparing 68 Gy to 78 Gy. International Journal of Radiation Oncology*Biology*Physics 61:1019–1034, 2005

26. Hoskin PJ, Rojas AM, Ostler PJ, et al: Randomised trial of external-beam radiotherapy alone or with high-dose-rate brachytherapy for prostate cancer: Mature 12-year results. Radiother Oncol 154:214–219, 2021

27. Dearnaley D, Syndikus I, Mossop H, 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 17:1047–1060, 2016

28. Rodda S, Tyldesley S, Morris WJ, et al: ASCENDE-RT: An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer. International Journal of Radiation Oncology*Biology*Physics 98:286–295, 2017