

Assessment of Toxicity After ^{68}Ga -PSMA-PET-Imaging Based Treatment Planning and Dose-Escalation in Radiation Therapy in Prostate Cancer Patients

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Abstract

PURPOSE: Effective tumor control in prostate cancer demands elevated radiation doses given its low alpha/beta ratio. We investigated in primary and recurrent prostate cancer whether dose-escalated-radiation therapy (DE-RT) based on ^{68}Ga -PSMA-PET positive lesions yields increased toxicity.

METHODS: We evaluated 90 patients (salvage DE-RT: 67 patients, DE-re-RT: 11 patients, definite DE-RT: 12 patients) who were treated based on a pre-treatment hybrid ^{68}Ga -PSMA. Findings from pre-treatment hybrid ^{68}Ga -PSMA-PET could result in an adaption of radiation planning. Common Toxicity Criteria of Adverse Effects (Version 4.03) were used to assess toxicity, this was done before the initiation and at the end of DE-RT, as well as at the first and last follow-up (F/U) examination. We evaluated the change in toxicity for each interval for the collective as well as in a per-patient analysis.

RESULTS: Findings in ^{68}Ga -PSMA-PET-imaging resulted in a change of TNM-stage in 61.1% and an adapted treatment concept in 71.1% of patients. When comparing overall toxicity before DE-RT and at the last follow-up, 5.9% treatment-related side effects (grade 1-3) occurred with 1.7% of them being severe (grade 3). In a patient-centered approach we examined the intra-individual changes in toxicity before and after DE-RT. At the last F/U, the majority out of 80 patients (range: 61.3-93.8%) stated unchanged toxicity rates compared to the toxicity examined at the initiation of RT.

CONCLUSION: The rate of treatment-related toxicity (grade 1-2) due to DE-RT in our cohort is 4.2%. For grade 3 toxicity it is 1.7%, respectively. The overall level of toxicity is highest during and shortly after completion of DE-RT (+7.4%) and improves over time until the last reported F/U (+5.9%). Compared to historical data, the toxicity profile of DE-RT is not increased. Therefore it is possible to apply DE-RT with the aim to increase tumor control by precisely treating all involved areas according to PSMA-PET-imaging.

Introduction

Prostate cancer (PC) is a major medical and socio-economic challenge worldwide [1]. It is the second most commonly diagnosed tumor in men with over 1.2 million new cases per year (as of 2018) [2].

At the same time, PC is a well treatable disease with a 5-year survival rate of 91% and a lifetime mortality risk of 3.3% [2]. The possibility of an earlier diagnosis through steady improvements in tumor diagnostics and the continuous improvements in treatment options have resulted in a decline in mortality in recent decades [1]. Nevertheless, PC ranks fifth concerning cancer-related death among men worldwide [3].

Radiation therapy (RT) for PC, in the primary setting as well as in a relapsed situation relies crucially on accurate clinical as well as imaging-based tumor staging. To differentiate between local, regional, or systemic disease, pre-treatment staging provides the basis for further treatment decisions and enables risk group-adapted treatment. To improve the outcome of PC patients after RT (e.g. progression-free survival, quality of life) individual diagnosis and tailored therapy planning is of utmost importance. Yet, conventional imaging yields low sensitivity for detection of small PC cancer deposits [4]. In recent years ^{68}Ga -PSMA-PET-imaging has proven to be more accurate for PC staging compared to conventional imaging including Choline and FACBC-PET-imaging [4–9]. Therefore ^{68}Ga -PSMA-PET-imaging has become the preferred imaging modality in recurrent PC for localization of disease extent and therapy planning of PC according to European guidelines [10–13]. In the planning process of definitive RT it has not yet become a standard tool [14]. With a very low alpha/beta ratio between 0.47 and 4.14, PC tumor control demands elevated radiation doses in order to annihilate all present cancer cells [15]. However, dose escalation entails an increased risk for side effects. Since most treatments are of curative nature, this demands an effective but equally tolerable treatment minimizing the likelihood of severe acute or chronic side effects. Moderate hypofractionation is a possibility to combine both aims as previously clinically shown [15–20].

The present work is to evaluate whether ^{68}Ga -PSMA-PET-imaging based dose-escalated (DE)-RT to all visible lesions entails increased toxicity for the patient or if these concept- and target volume changes are feasible with acceptable side effect rates in patients treated with definitive or salvage RT for PC.

Methods

We evaluated 90 patients with histologically proven PC that were treated with DE-RT based on a ^{68}Ga -PSMA-PET/CT or ^{68}Ga -PSMA-PET/MRI between 2013 and 2016. 67 patients (74.4%) were treated with an intensified salvage RT concept after radical prostatectomy and 11 patients (12.2%) received an intensified second RT (DE-re-RT) after a previous resection and RT. Here patients received a RT of the pelvic lymph drainage including a boost to affected lymph nodes after a previous RT of the prostate bed as an annexation of the previous radiation volume. 12 patients (13.3%) received a definite DE-RT. Patient characteristics are shown in Table 1.

Table 1
Patient characteristics for dose-escalated radiation therapy (DE-RT)

	all patients	DE-RT after surgery	DE-re-RT after surgery	definite DE-RT
number of patients n (%)	90	67 (74.5)	11 (12.2)	12 (13.3)
age at RT				
median (range)	70 (48–88)	69 (50–78)	70 (51–75)	74 (48–88)
iPSA (ng/ml)				
median	11.0	10.2	17.0	14.0
(range)	(1.4–211.7)	(1.4–56.1)	(4.1–82.1)	(6.5–211.7)
PSA at PSMA-PET (ng/ml)				
median	1.3	0.9	1.8	14.0
(range)	(0.1–211.7)	(0.1–14.7)	(0.2–11.7)	(1.1–211.7)
tumor stage n (%) (post surgery = pT, definite = cT)				
T1c	1 (1.1)	0 (0.0)	0 (0.0)	1 (8.3)
T2a	4 (4.4)	3 (4.5)	1 (9.1)	0 (0.0)
T2b	3 (3.3)	2 (3.0)	0 (0.0)	0 (0.0)
T2c	19 (21.1)	13 (19.4)	2 (18.2)	4 (33.3)
T2x	2 (2.2)	2 (3.0)	0 (0.0)	0 (0.0)
T3a	20 (22.2)	18 (26.9)	1 (9.1)	1 (8.3)
T3b	32 (35.6)	23 (34.3)	6 (54.5)	3 (25.0)
T3x	1 (1.1)	1 (1.5)	0 (0.0)	0 (0.0)
T4	4 (4.4)	2 (3.0)	1 (9.1)	0 (0.0)
unknown	4 (4.4)	3 (4.5)	0 (0.0)	1 (8.3)
N0	44 (48.9)	37 (55.2)	6 (54.5)	1 (8.3)
N1	41 (45.6)	26 (38.8)	5 (45.5)	10 (83.3)
unknown	5 (5.6)	4 (6.0)	0 (0.0)	1 (8.3)
M0	44 (48.9)	32 (47.8)	5 (45.5)	7 (58.3)
M1a	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
M1b	2 (2.2)	1 (1.5)	0 (0.0)	1 (8.3)
M1c	1 (1.1)	0 (0.0)	1 (9.1)	0 (0.0)
Mx	43 (47.8)	34 (50.7)	5 (45.5)	4 (33.3)
R0	40 (50.6)	35 (52.2)	5 (45.5)	∅
R1	29 (36.7)	23 (34.3)	6 (54.5)	∅
unknown	10 (12.7)	9 (13.4)	0 (0.0)	∅
Gleason Score n (%)				
6	3 (3.3)	1 (1.5)	0 (0.0)	2 (16.7)
7	48 (53.3)	41 (61.2)	4 (36.4)	3 (25.0)
8	15 (16.7)	8 (11.9)	2 (18.2)	5 (45.5)
9	20 (22.2)	14 (20.9)	5 (45.5)	1 (8.3)
10	1 (1.1)	0 (0.0)	0 (0.0)	1 (8.3)
unknown	3 (3.3)	3 (4.5)	0 (0.0)	0 (0.0)
D'Amico risk group n (%)				

	all patients	DE-RT after surgery	DE-re-RT after surgery	definite DE-RT
low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
intermediate	6 (6.7)	5 (7.5)	0 (0.0)	1 (8.3)
high	81 (90.0)	59 (88.1)	11 (100.0)	11 (91.7)
unknown	3 (3.3)	3 (4.4)	0 (0.0)	0 (0.0)
lymph node risk according to Roach (%)				
mean ± std dev	28.8 ± 19.1	25.4 ± 12.8	36.6 ± 18.4	41.8 +/- 36.1
(range)	(3.5–100.0)	(3.5–66.1)	(12.9–74.7)	(4.3–100.0)

All patients were documented and followed prospectively within the institutional database. All gave written informed consent for the purpose of anonymized evaluation and publication of their data. All reported investigations were conducted in accordance with the Helsinki Declaration and with national regulations. This analysis from the database was approved by the Ethics Committee of the Technical University of Munich (TUM) with the permit 121/17S.

Synthesis of ⁶⁸Ga-PSMA-11 and technical details on the performance of ⁶⁸Ga-PSMA-PET/CT or ⁶⁸Ga-PSMA-PET/MRI are previously described [6, 8, 9]. Findings from pre-treatment hybrid ⁶⁸Ga-PSMA-PET could result in an adaption of radiation planning [11] compared to results of standard imaging and clinical risk factors (TNM classification, Gleason score, risk according to Roach [21] and D'Amico [22]).

All cases were discussed in consensus in an interdisciplinary tumor board consisting of at least one experienced radiation oncologist, radiologist, nuclear medicine physician and urologist.

In our department the radio-oncological planning target volume (PTV) is generated according to the RTOG consensus. The exact definition of clinical target volume (CTV) and PTV in the context of definite RT [14] and salvage RT [23] has been published. Depending on the additionally obtained results of the ⁶⁸Ga-PSMA-PET the RT concept and volume were adapted. For patients who received a salvage or a re-RT all PSMA-PET positive areas were treated with a dose escalation. For patients who received a definite RT the prostate was treated with a uniform dose and dose-escalation was only applied to PSMA-PET-positive lymph nodes. The exact dosage and fractionation are shown in Table 2.

Table 2
Dosage and fractionation for dose-escalated radiation therapy (DE-RT). DE-RT was applied based on simultaneously integrated boost (SIB) concepts

	Prostate	Prostate bed	PET-positive-lesion within the prostate bed	Lymphatic drainage	PET-positive- lymph nodes
Dose (Gy)	76.5	68	76.5 via SIB	50.4	58.8 or 61.6 via SIB
Fractions	34	34	34	28	28

The following constraints were used:

- bladder: V40 < 40%, V50 < 30%, V70 < 20%
- rectum: V40 < 40%, V65 < 35%, V50 < 30%, V70 < 20%, V75 < 15%
- sigmoid: Dmax 60 Gy
- colon: Dmax 55 Gy
- small intestine: Dmax 50 Gy, < 10 ml over 50 Gy, < 135 ml over 45 Gy
- femoral heads: Dmean < 25 Gy
- genital: As low as rationally achievable (ALARA)
- penile bulb: Dmean < 50 Gy

All patients received an intensity-modulated radiotherapy (IMRT). RT was performed on one of the two types of linear accelerators (Clinac® radiation devices (Varian® Medical systems Incorporated, Palo Alto, CA, USA)) and the TomoTherapie® radiation device (Accuray® Incorporated, Sunnyvale, CA, USA). The treatment was performed with a reproducible comfortably filled bladder and empty rectum under daily image guidance.

We collected data for toxicity before the initiation and at the end of DE-RT, as well as at the first and last follow-up (F/U) examination.

Generally, F/U visits were scheduled at 6 weeks post radiation, then time intervals were prolonged to three months and six months before continuing on an annual basis. In the case of unexpectedly increased side effects, shorter intervals were scheduled by the treating physician. Documentation and classification were done according to American National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 [24], wherever applicable. Missing data was obtained by contacting the outpatients' urologist whenever possible.

As part of the CTCAE listed toxicity, gastrointestinal (GI) (diarrhea, proctitis) and urogenital (UG) (cystitis, incontinence, urinary urge) as well as erectile dysfunction were assessed. Aside from that, libido, nocturia and status of catheterization was documented. Grading for these was done as follows; For nocturia: grade 1 = every 4 hours (1–2 times a night), grade 2 = every 2–3 hours (3–6 times a night), grade 3 = every 1–2 hours (> 6 times a night); For libido:

grade 0 = normal sexual desire, grade 1 = reduced sexual desire, grade 2 = no sexual desire. Additionally, the patients' status of catheterization was documented (0 = no catheterization, 1 = catheterization).

All toxicity that occurred within three months after completion of RT was classified as *acute* and all toxicity that occurred thereafter was classified as *chronic*.

We evaluated the change in toxicity for each interval between the initiation of DE-RT, the first F/U visit and the last F/U visit. In order to calculate each value, the percentage of patients showing a side effect at the earlier visit was subtracted from the percentage of the patients showing the same side effect at the later visit. Furthermore, we conducted a per-patient-analysis of the intra-individual changes in toxicity over time using a log-rank test. All statistical analyses were performed descriptively with exploratory intention using proportions and means.

Results

Findings in ⁶⁸Ga-PSMA-PET-imaging resulted in a change of TNM-stage in 61.1% and an adapted treatment concept in 71.1% of patients. In most of these cases (salvage DE-RT: 73.1%, DE-re-RT: 81.8%, definite DE-RT: 41.7%) no morphological correlate for the PSMA-PET-positive finding was present on conventional imaging. A total of 48 patients (53.3%) received androgen-deprivation-therapy (ADT) during DE-RT.

Table 3 shows findings in ⁶⁸Ga-PSMA-PET-imaging.

Table 3
Findings of the ⁶⁸Ga-PSMA-PET/CT or ⁶⁸Ga-PSMA-PET/MRI

	Out of all treatment groups	DE-RT after surgery	DE-re-RT after surgery	definite DE-RT
n	90	67	11	12
PSMA PET results n (%)				
new lesions (NL) only present in PET	63 (70.0)	49 (73.1)	9 (81.8)	5 (41.7)
change of stage due to NL	55 (61.1)	43 (64.2)	8 (72.7)	4 (33.3)
change of therapy due to NL	64 (71.1)	49 (73.1)	9 (81.8)	6 (50.0)
positive local finding:	59 (65.6)	47 (70.1)	0 (0.0)	12 (100.0)
no correlate in CT/MRI	32 (35.6)	30 (44.8)	0 (0.0)	2 (16.7)
positive lymph node(s) (LN):	62 (68.9)	43 (64.2)	10 (90.9)	11 (91.7)
no correlate in CT/MRI	42 (44.4)	29 (43.3)	9 (81.8)	3 (25.0)

At the first F/U visit after RT the presence of acute toxicity was assessed in 89 patients. One patient was lost to F/U. The presence and change in chronic toxicity were analyzed at the last F/U after a median of 20.1 months (interquartile: 12.0-30.8 months) in 80 patients. 9 patients participated only in the first F/U appointment after RT.

Toxicity rates at first and last F/U

Acute and late side effects are illustrated in Table 4. A total of 30 patients (21.5%) reported acute GI toxicity (grade 1–3) after DE-RT. The majority of patients (78.6%) stated side effects to be nonexistent or only mild (grade 1). Only three patients (3.4%) reported severe, CTCAE grade 3 side effects (grade 3 diarrhea: 1, grade 3 proctitis: 2). Chronic GI side effects occurred in 22 patients (27.5%). Two cases (2.5%) were assessed as severe grade 3 proctitis.

Table 4
Gastrointestinal (GI) and urogenital (UG) toxicity at different points in time: initiation of radiation therapy (n = 90), first follow-up visit after RT (1. F/U, n = 89) and last follow-up after a median of 20.1 months (last F/U, n = 80)

Maximum degree of acute toxicity for each patient	Before RT		1. F/U		Last F/U	
	GI, n (%)	UG, n (%)	GI, n (%)	UG, n (%)	GI, n (%)	UG, n (%)
0	80 (88.9)	7 (7.8)	61 (68.5)	2 (2.3)	58 (72.5)	1 (1.3)
1	3 (3.3)	8 (8.9)	9 (10.1)	13 (14.6)	8 (10.0)	10 (12.5)
2	5 (5.6)	23 (25.5)	18 (18)	16 (18)	12 (15.0)	12 (15.0)
3	2 (2.2)	52 (57.8)	3 (3.4)	58 (65.2)	2 (2.5)	57 (71.3)
4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Σ	90 (100)	90 (100)	89 (100)	89 (100)	80 (100)	80 (100)

Almost all patients (n = 87, 97.7%) reported UG side effects. Overall erectile dysfunction (grade 1–3) was found in 74 cases (92.5%). Grade 3 UG toxicity was exclusively caused by erectile dysfunction. Out of the 58 patients reporting grade 3 erectile dysfunction at the first F/U, 90% (n = 52) had reported the same

severity before the start of DE-RT and can therefore be accounted as non-treatment related. 48 patients were actively treated with ADT before/ during DE-RT. 5 new cases (6.25%) of grade 3 erectile dysfunction occurred up to the last F/U.

Change in toxicity

At the last F/U, the toxicity rates mostly improved compared to the toxicity examined at the first F/U-visit. Compared to the initiation of DE-RT, slightly higher levels of toxicity were observed.

Overall, an increase of 4.2% of side effects (grade 1–2) was reported. 1.7% of the reported side effects were severe (grade 3).

Change in toxicity before DE-RT and first F/U

Comparing the toxicity rates before the initiation of DE-RT and the first F/U visit, we found that 12% of our patients developed acute GI toxicity. GI Grade 3 side effects increased by 1.1%. Patients mostly developed grade 1 diarrhea (+ 10.1%) and grade 2 proctitis (+ 9.1%). UG toxicity (cystitis, nocturia and urinary urge) showed an increase of 12% at the first F/U. Except for erectile dysfunction which increased heavily by 8.5%, no new grade 3 UG toxicity (-0.73%) occurred up to the first F/U.

Change in toxicity between first and last F/U

Regarding the change of toxicity rates between the first F/U and the last F/U, we saw an improvement over time concerning side effects. The number of patients showing no more GI side effects increased by 2.3% at this point. At the same time GI grade 1–3 toxicity decreased by -0.4 to -1.5%.

The number of patients showing no more UG side effects increased by 1.3% at this point, with a decrease in grade 1 and 2 UG side effects (-1.7%/-0.8%) and a further increase in grade 3 toxicity to 1.2%. For post-radiogenic cystitis an improvement of + 18.0% patients not reporting any cystitis complaints (grade 0) was present.

Change in toxicity before DE-RT and last F/U

Concerning the overall toxicity change between the initiation of the DE-RT and the last F/U an amelioration towards the baseline can be observed for most of the reported toxicity. Side effects that appeared for the first time after RT (grade 1–3), alleviated or disappeared in a long-term perspective (range: -11.4% - + 1.1%). Compared to the initiation of DE-RT, GI toxicity was still present in + 9.6% patients (average decline 2.3%). UG toxicity was still present in + 9.9% to + 1.8% patients. Exceptions were acute cystitis that showed a recovery to above the baseline (1.1% more patients not presenting this toxicity) and erectile dysfunction that worsened over time (11.4% more patients showing symptoms with 14.6% more patients being grade 3). The complete data can be found in table 5.

Table 5: Differences (Δ) in toxicity and overview over the distribution of each toxicity by grades before the initiation of the radiation therapy (1. RT), the first and last follow-up visit (F/U) and overview over the distribution of each toxicity by grades

toxicity	grade 0		grade 1		grade 2		grade 3		grade 0		grade 1		grade 2		grade 3
	n (%) at 1. RT	r 1. F/U - 1. RT	n (%) at 1. F/U	r last F/U - 1. F/U	n (%) at 1. F/U	r last F/U - 1. F/U	n (%) at 1. F/U	r last F/U - 1. F/U	n (%) at 1. F/U						
gastrointestinal (GI)															
proctitis	82 (91.1)	-12.5%	1 (1.1)	1.1%	7 (7.8)	9.1%	0	2.2%	70 (78.7)	2.6%	2 (2.3)	-1.0%	15 (16.9)	-1.9%	2 (2.3)
diarrhea	86 (95.6)	-11.3%	2 (2.2)	10.1%	0	2.2%	2 (2.2)	-1.1%	75 (84.3)	2.0%	11 (12.4)	0.1%	2 (2.3)	-1.0%	1 (1.1)
average		-11.9%		5.6%		5.7%		0.6%		2.3%		-0.4%		-1.5%	
urogenital (UG)															
cystitis	71 (78.9)	-16.0%	9 (10.0)	11.3%	9 (10.0)	5.7%	1 (1.1)	-1.1%	56 (62.9)	17.1%	19 (21.4)	-13.8%	14 (15.7))	-5.7%	0
stress incontinence	56 (62.2)	4.1%	15 (16.7)	-3.2%	19 (21.1)	-0.9%	0	0.0%	59 (66.3)	-8.8%	12 (13.5)	6.5%	18 (20.2)	2.3%	0
nocturia	31 (34.4)	-9.7%	50 (55.6)	2.9%	8 (8.9)	8.0%	1 (1.1)	-1.1%	22 (24.7)	5.3%	52 (58.4)	-7.2%	15 (16.9)	1.9%	0
urinary urge	73 (81.1)	-10.3%	15 (16.7)	9.2%	2 (2.2)	1.1%	0	0.0%	63 (70.8)	0.5%	23 (25.8)	2.9%	3 (3.4)	-3.4%	0
libido	86 (95.6)	-2.3%	3 (3.3)	2.3%	1 (1.1)	0.0%	n/a	n/a	83 (93.3)	0.5%	5 (5.6)	0.6%	1 (1.1)	-1.1%	n/a
erectile dysfunction	17 (18.9)	-5.4%	8 (8.9)	0.1%	14 (15.6)	-3.2%	51 (56.7)	8.5%	12 (13.5)	-6.0%	8 (9.0)	-0.2%	11 (12.4)	0.1%	58 (65.2)
catheterization	88 (97.8)	-3.4%	2 (2.2)	3.4%	n/a	n/a	n/a	n/a	84 (94.4)	0.6%	5 (5.6)	-0.6%	n/a	n/a	n/a
average		-6.1%		3.7%		1.5%		0.9%		1.3%		-1.7%		-0.8%	
overall		-7.4%		4.1%		2.5%		0.8%		1.5%		-1.4%		-1.0%	

Per-patient analysis

In a per-patient analysis we examined the intra-individual changes in toxicity over time. At the last F/U, the majority out of 80 patients (range: 61.3–93.8%) showed unchanged toxicity rates compared to the toxicity examined before the initiation of DE-RT.

The level of proctitis remained unchanged in 66 patients (73.3%). It increased by up to three degrees in 11 patients (13.8%) and decreased by two degrees of toxicity in three patients (3.8%).

The level of diarrhea remained unchanged in 68 patients (85.0%). It increased by a maximum of one degree in nine cases (11.3%). An improvement of up to three levels of toxicity was reported in 3 cases (3.8%) (Fig. 1).

Before the start of RT, 19 (21.1%) patients reported cystitis; 80% of patients showed no change concerning this toxicity at the time of the latest F/U. An increase of up to three degrees of severity occurred in seven cases (8.9%), simultaneously there was a decrease of up to two degrees of severity in 9 cases (11.3%) (Fig. 2). Stress incontinence (up to grade 2) was documented in 34 cases (37.8%) before RT. Up to the last F/U examination, there was no change in the degree of side effects in 60 cases (75%). For urinary urge and nocturia 17 (18.9%) respectively 59 (65.6%) patients showed at least grade 1 toxicity before the RT. Here unchanged rates were seen in 68.8% and 61.3% of the cases (shown in Fig. 2).

At the time of the last F/U, 75 patients (93.8%) reported no change in libido. At the beginning of RT, 73 patients (81.2%) reported having an erectile dysfunction, in 51 cases (56.7%) the potency had completely disappeared.

At the time of the last F/U examination, unchanged erectile dysfunction was reported in 55 cases (68.8%). In eight patients (10.0%) the potency in the case of normal erectile function before radiotherapy was completely gone at the time of the last F/U examination (shown in Fig. 3).

Discussion

Prostate Cancer cell eradication demands elevated radiation doses. In order to minimize side effects, such as urine-, bowel- and sexual-dysfunction, we conducted a ⁶⁸Ga-PSMA-PET planned DE-RT study with the aim of increasing tumor control while achieving acceptable side effects. In this paper the radiation induced toxicity is highlighted.

In our investigated group of 90 patients that received a ⁶⁸Ga-PSMA-PET planned DE-RT, acute side effects showed an inhomogeneous distribution with regard to the degree of manifestation of GI and UG toxicity. In 78.6 % of the patients no or only mild GI side effects up to grade 1 were found. Acute, above baseline, grade 3 UG toxicity was found in 6.7%. A high number of patients reporting erectile dysfunction (58 cases) can be explained by the inclusion of patients with previous radical prostatectomy in 42 cases and ongoing ADT in 48 cases. These were therefore most likely not treatment-related. Aside from erectile dysfunction no grade 3 UG toxicity is reported. 57.3% of the patients developed grade 2 toxicity and 42.7% of the patients presented with no or only mild grade 1 toxicity. Concerning chronic GI side effects only 2 cases of grade 3 proctitis were seen.

In order to answer the question if DE-RT concepts, as used in our study, come at an increased risk for patients concerning side effects, we looked at reported outcomes of conventionally planned and normo-fractionated RT studies. Abundant comparative information on toxicity rates for acute UG side effects was collected in the context of hypo-fractionated studies such as the Italian- [25], the CHHiP- [26] or the HYPRO-Trial [27–29]. Acute UG toxicity of at least grade 2 were observed in the conventionally fractionated arm in 40% – 58% of patients. This is comparable to the range of our numbers.

In a retrospective, two-institutional analysis 90 patients with biochemical recurrence, who received ⁶⁸Ga-PSMA-PET-CT before DE-RT were examined. Patients received 70 Gy for local PET-positive tumor lesions, 66 Gy were applied in the prostatic bed, PET-positive lymph nodes received 60.8 Gy, and the pelvic lymph drainage 50.4 Gy. After a median F/U of 23 months, 2 patients had late grade 3 UG toxicity, GI grade 3 toxicity or higher did not occur [30, 31].

Another study of ⁶⁸Ga -PSMA-PET planned Salvage-RT for high-risk patients by Zschaeck et al. also reported low post-radiation toxicity. After having received a boost to PSMA-positive lesions (tumor lesions: 74 to 77.7 Gy, lymph nodes: 66 Gy, bone lesions: 42–66 Gy while the prostate bed received 66 Gy and the lymphatic drainage 54 Gy) only 2 out of 21 patients showed acute toxicity greater than grade 1. No late toxicity greater than grade 1 was reported with a median F/U time of 29 months [12].

This is also confirmed in a similar form in other studies. An Australian retrospective study by Shakespeare et al. investigated the efficiency and side effects of a PSMA-PET planned definite DE-RT in a cohort of 46 high-risk PC patients with only lymph node metastasis using an escalated dose of 81 Gy (single dose: 1.8 Gy) to the prostate and affected lymph nodes (lymphatic drainage: 60 Gy) showing promising results: After a median F/U of two years, there was an excellent tolerance of the RT. Acute grade 1 or 2 GI toxicity was found in 48%/11% of the patients, and UG toxicity in 72%/24%. Late grade 1–3 GI toxicity was still present in 13%/2%/0% of the cases and UG toxicity in 28%/13%/4%. None of the toxicity correlated with dose escalation to PET positive lymph nodes [32].

Despite different numbers of patients, different dosing concepts and larger variety of treatment indications, our numbers are also comparable to other DE-RT studies and show even lower acute grade 1 and 2 toxicity (GI: 10.1%/18%, UG: 14.6%/18%) as well as mostly the same late grade 1–3 toxicity (GI: 10%/15%/2.5%, UG: 12.5%/15%/71.3%). Again, our UG grade 3 toxicity must be understood in the context of the already pre-existing erectile dysfunctions.

Examining the change of side effects, above baseline, before the initiation of RT to the first and last F/U more closely, for the majority of the toxicity reported we found an initially quick deterioration, followed by a slower recovery to an overall comparably unchanged end result. This means that the increase of side effects attributable to the radiation itself is non-existent to mild.

On average, at the first F/U 7.4% of the toxicity appeared for the first time due to DE-RT. Most of it being grade 1 and 2 (6.6%). An amelioration over time occurred so that at the last F/U 5.9% more patients reported a side effect that was not present before RT. This was mainly caused by proctitis (9.9%), urinary urge symptoms (9.9%) and diarrhea (9.1%).

Cystitis, being one of the most common radiogenic side effects in pelvic irradiation, is a good example of illustrating worsening and improvement over time: At the first F/U an increase of 16% was seen, but ultimately at the last F/U the rate had completely returned to the baseline.

Upon an individual per-patient analysis, the majority out of 80 patients showed overall unchanged toxicity rates; Patients stated that libido (93.8%), diarrhea (85%), cystitis (80%), stress incontinence (75%) and proctitis (73.3%) were unchanged by DE-RT. For nocturia (23.8%), erectile dysfunction (22.5%) and urinary urge (20%) an aggravation or onset of symptoms of at least 1 had occurred. Contrary to this, in other patients improvements beyond the initial status were seen (nocturia (15%), cystitis (11.3%), urinary urge (11.3%)).

As part of the ProtecT-study, the post-therapeutic GI and UG side effects and quality of life were assessed and compared six months, twelve months and every year after active surveillance, RPE or definite RT among 1,643 patients with localized PC. The severity and recovery time differed in all three groups. After RT the sexual function recovered steadily from six months after RT and stabilized over the course of the six years; also, RT had little effect on urinary continence. In contrast, bowel function, urinary retention and nocturia were worst six months after RT, while it was unchanged in the other groups. Over the course of time, however, most of the intestinal and micturition function stabilized after RT [33]. In contrast to the ProtecT study, our patients had multiple RT indications (post-operatively, re-salvage next to definite), thus a different history and other symptoms at the beginning of the RT. Nevertheless, the side effects after our DE-RT behaved comparably to the conventionally fractionated RT in the ProtecT study. In particular, GI toxicity, nocturia and urinary urge showed the described rapid deterioration with slow recovery towards a stable result. With a shorter F/U period than the ProtecT study (6 years) up to now, a further improvement in our cohort could be expected.

The Cochrane analysis by Daly et al. supports these results. The review of three randomly controlled studies showed increased acute and late GI side effects, urinary strictures and incontinence after adjuvant RT compared to only RPE, but in the long run there was hardly any moderate to severe toxicity [34].

There are limitations to our study. We carried out a retrospective study with an inhomogeneous patient population. Our patients were in different stages of their illness, had different treatments beforehand and therefore different side effect profiles. This includes anti-hormonal therapy, which was taken by part of our patients throughout the timeframe of this study. On the other hand, this study represents a broad overview and a real-life-collective.

Also, to evaluate the superiority of ^{68}Ga -PSMA-PET-planned DE-RT, prospective studies would be favorable. A comparison with a conventionally treated control group would be desirable, but essentially impossible because of ethical and patient preference reasons.

Last, an analysis of biochemical progression free survival of this cohort is to follow.

Conclusions

For acute and chronic toxicity rates, as well as for change in toxicity analysis, we see the majority of patients reporting no or only mild toxicity. The rate of new appearing toxicity in our study population is below 5% for grade 1–2 and below 2% for grade 3.

In most cases, DE-RT could be performed without an increase in long-term toxicity and we postulate ^{68}Ga -PSMA-planned DE-RT to be tolerable with acceptable side effects.

In summary, we see great potential for ^{68}Ga -PSMA-PET planned DE radiation concepts. It is possible to use essentially high radiation doses for tumor control by precisely treating all involved areas and thereby potentially sparing uninvolved areas from unnecessary toxicity. Compared to existing literature, we see that radiation volumes with elevated radiation dose (boost) to affected lymph nodes or within the prostate region are not producing more acute and long-term toxicity throughout all examined gastrointestinal and urogenital parameters and could therefore be used safely on a more regular basis. Finally, and seen in increasingly more studies, PSMA-PET planned DE radiation concepts and volumes can potentially translate into improved local control and/or overall survival for our patients. This will be analyzed for this study cohort of patients in a study to follow.

Declarations

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This analysis from the database was approved by the Ethics Committee of the Technical University of Munich (TUM) with the permit 121/17S.

CONSENT FOR PUBLICATION

All authors agree for publication.

AVAILABILITY OF SUPPORTING DATA

The data and material can be accessed by contacting the corresponding authors

COMPETING INTERESTS

On behalf of all authors, the corresponding author states that there is no conflict of interest.

FUNDING

Not applicable

AUTHORS' CONTRIBUTIONS

KS made substantial contributions to conception and design, analysis and interpretation of data, involved in drafting the manuscript, revised it critically for important intellectual content, gave final approval of the version to be publish; agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

SD made substantial contributions to conception and design, analysis and interpretation of data, involved in drafting the manuscript, revised it critically for important intellectual content, gave final approval of the version to be publish; agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

LP made substantial contributions to conception and design, acquisition of data and analysis; agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

MMEV revised it critically for important intellectual content, gave final approval of the version to be publish; agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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MD revised it critically for important intellectual content, gave final approval of the version to be publish; agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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JEG revised it critically for important intellectual content, gave final approval of the version to be published; agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

SEC revised it critically for important intellectual content, gave final approval of the version to be published; agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figures

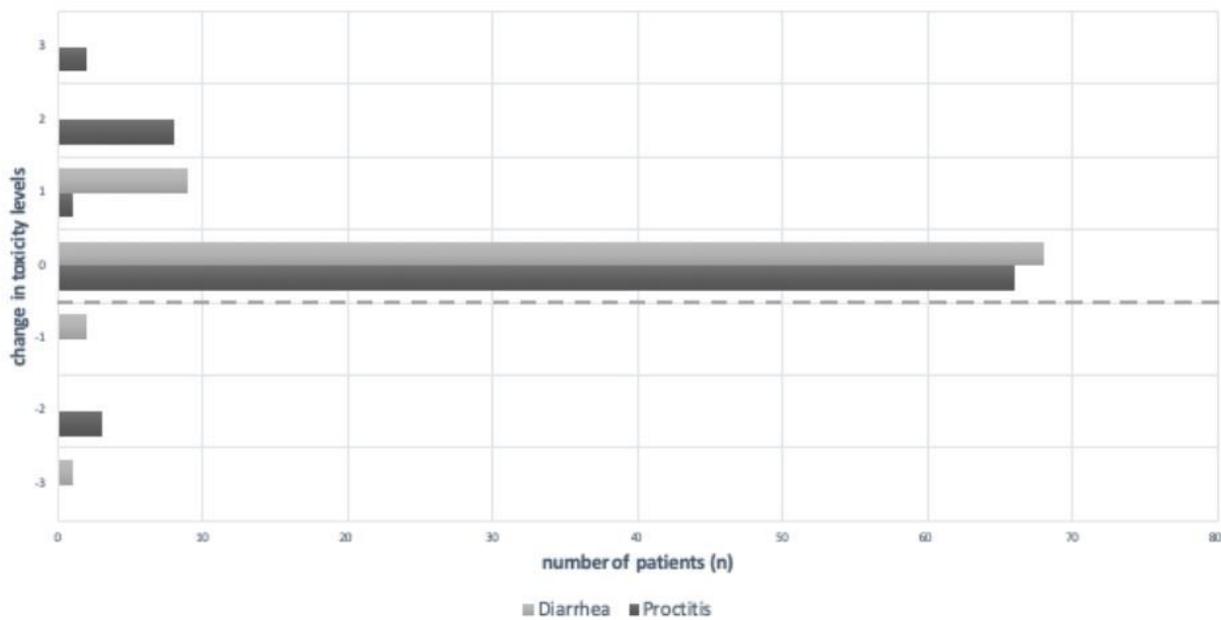


Figure 1

Increase/decrease between the initiation of the radiation therapy and the last follow-up for gastrointestinal toxicity

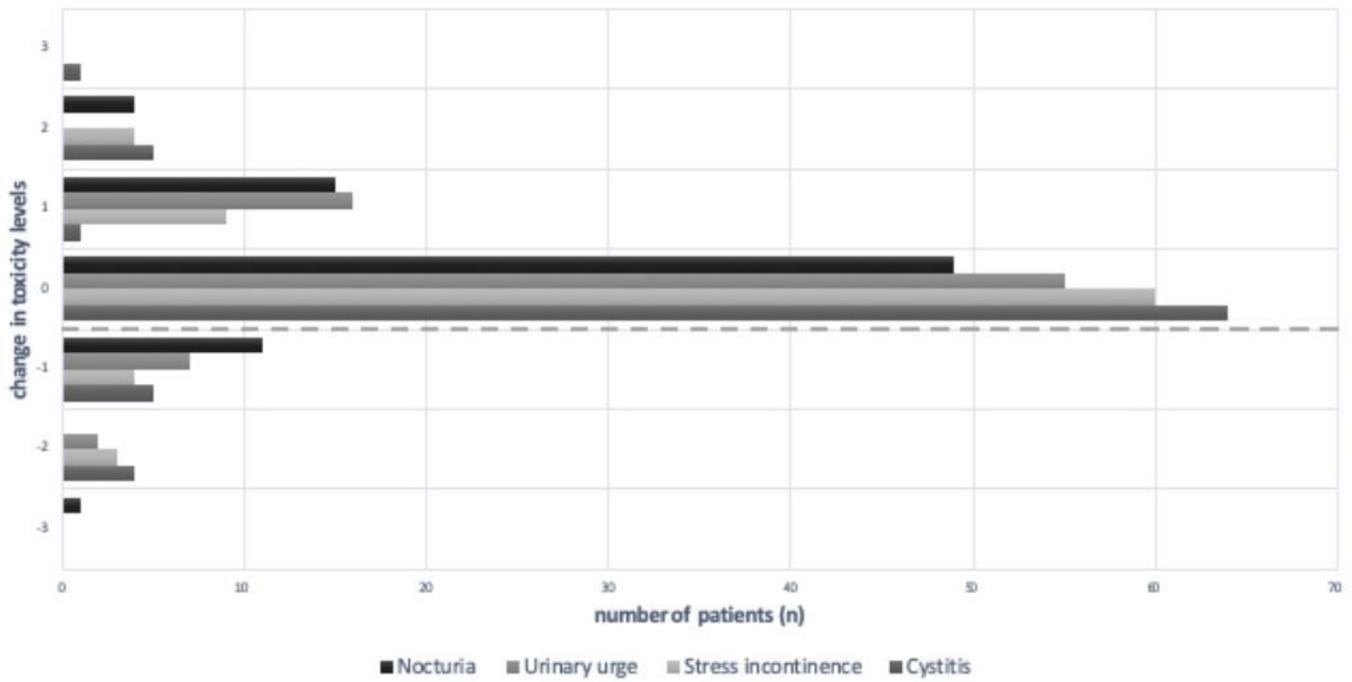


Figure 2

Increase/decrease between the initiation of the radiation therapy and the last follow-up for urogenital toxicity (1)

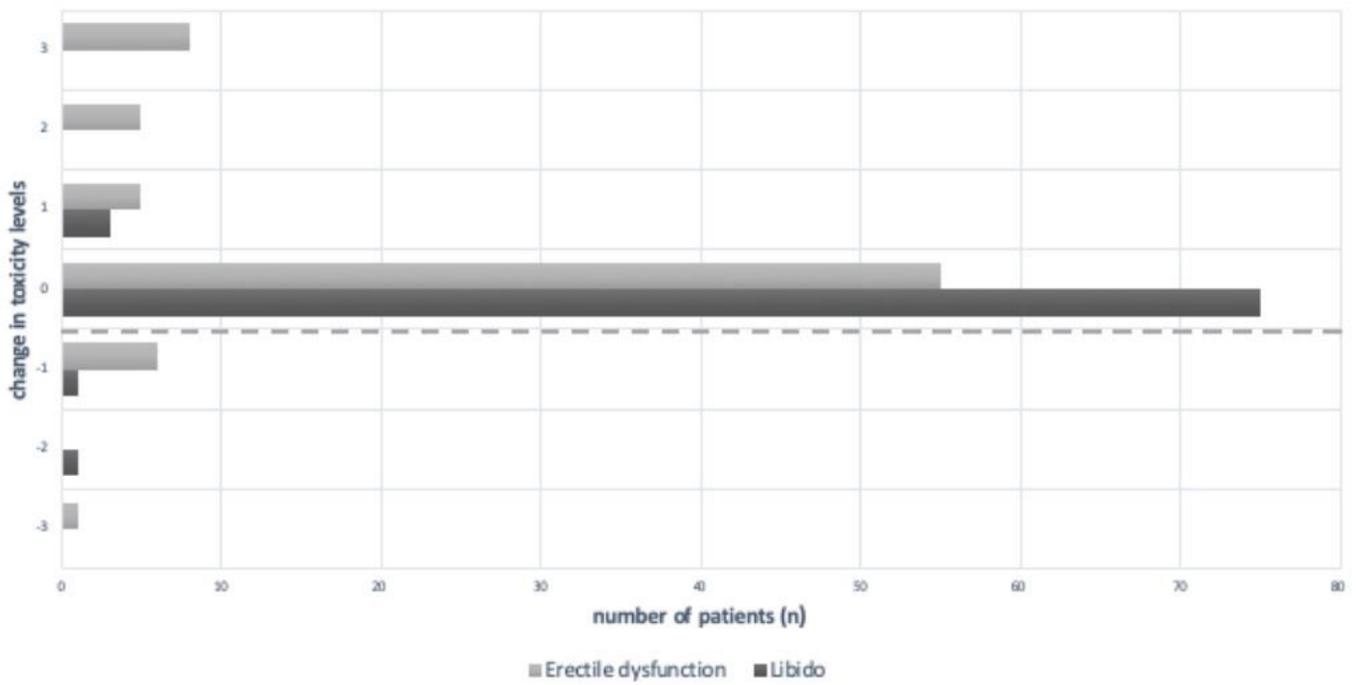


Figure 3

Increase/decrease between the initiation of the radiation therapy and the last follow-up for urogenital toxicity (2)