Journal of Nuclear Medicine, published on July 12, 2018 as doi:10.2967/jnumed.118.212563

Outcome after PSMA PET/CT based salvage radiotherapy in patients with biochemical recurrence after radical prostatectomy: a bi-institutional retrospective analysis

Short running title: PSMA PET/CT based salvage radiotherapy

Dr. med. Nina-Sophie Schmidt-Hegemann [1], Prof. Dr. med. Christian Stief [2], Tak-Hyun Kim [3], Chukwuka Eze [1], Dr. med. Simon Kirste [3], Iosif Strouthos [3], Dr. med. Minglun Li [1], Prof. Dr. med. Wolfgang Schultze-Seemann [4], Dr. med. Harun Ilhan [5], PD Dr. med. Wolfgang Peter Fendler [6], Prof. Dr. med. Peter Bartenstein [5], Prof. Dr. med. Anca-Ligia Grosu [3,7], Prof. Dr. med. Ute Ganswindt [8], Prof. Dr. med. Claus Belka [1,9], Prof. Dr.med Dr. Philipp T. Meyer [10], Dr. med. Constantinos Zamboglou [3,7,11]

1) Department of Radiation Oncology, University Hospital, LMU Munich
2) Department of Urology, University Hospital, LMU Munich
3) Department of Radiation Oncology, Medical Center – University of Freiburg, Faculty of Medicine. University of Freiburg, Germany
4) Department of Urology, Medical Center – University of Freiburg, Faculty of Medicine. University of Freiburg, Germany
5) Department of Nuclear Medicine, University Hospital, LMU Munich
6) Department of Nuclear Medicine, University Hospital Essen
7) German Cancer Consortium (DKTK). Partner Site Freiburg, Germany
8) Department of Therapeutic Radiology and Oncology, Innsbruck Medical University, Austria
9) German Cancer Consortium (DKTK). Partner Site Munich, Germany
10) Department of Nuclear Medicine, Medical Center – University of Freiburg, Faculty of Medicine. University of Freiburg, Germany
11) Berta-Ottenstein-Programme, Faculty of Medicine, University of Freiburg, Germany

* Corresponding author:
Dr. med. Nina-Sophie Schmidt-Hegemann
Department of Radiation Oncology, University Hospital, LMU Munich
Marchioninistr. 15, 81377 Munich, Germany
Tel: +49 89 4400 73770
Fax: +49 89 4400 76770
E-mail address: Nina-Sophie.Hegemann@med.uni-muenchen.de

ABSTRACT

Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) detects prostate cancer recurrence at low PSA levels. Radiotherapy with dose escalation to the former prostate bed has been associated with improved biochemical recurrence-free survival (BRFS). Thus, we hypothesized that PSMA PET/CT-guided salvage radiotherapy leads to improved BRFS. **Methods:** A total of 204 consecutive patients were referred for salvage radiotherapy following radical prostatectomy. PSMA PET/CT scans were performed and patients with PSA persistence (109 patients) or evidence of distant metastases (5 patients) were excluded from this analysis. Thus, the following analysis is based on a total of 90 patients who underwent PSMA PET/CT prior to radiotherapy due to biochemical recurrence and received salvage radiotherapy. In case of PET-positive findings, antiandrogen therapy was commenced before initiation of radiotherapy. BRFS (PSA ≤ 0.2 ng/ml) was defined as the study endpoint. **Results:** PET-positive lesions were detected in 42/90 (47%) patients: 24/42 (27%) fossa recurrence only, 12/42 (13%) pelvic lymph nodes only and 6/42 (7%) fossa and pelvic lymph node recurrence. Median PSA before radiotherapy was 0.44 (0.11 - 6.24). Cumulatively, a total dose of 70.0 Gy (67.2 - 72 Gy) was delivered to local macroscopic tumor, 66 Gy (59.4 - 70.2 Gy) to the prostatic fossa, 60.8 Gy (54 - 66 Gy) to PET-positive lymph nodes and 50.4 Gy (45 - 50.4 Gy) to the lymphatic pathways. After a median follow-up of 23 months, BRFS was 78%. Antiandrogen therapy was ongoing in 4 patients at last follow-up. No significant difference in BRFS between PET-positive (74%) vs. PET-negative patients (82%; $p>0.05$) was observed at last follow-up. Two patients had late genitourinary toxicity grade 3 and no patient had gastrointestinal toxicity ≥ 3 (NCI-CTCAE v4.03). **Conclusion:** PSMA PET/CT-guided salvage radiotherapy is an effective and safe local treatment option. No difference in BRFS between PET-positive and PET-negative patients was observed, indicating effective targeting of PET-positive lesions. PSMA PET/CT when readily available should be offered to patients with PSA recurrence for treatment individualization.

Key Words: prostate cancer, PSMA PET/CT, biochemical recurrence, radiotherapy

INTRODUCTION

Almost 30% of prostate cancer (PCa) patients have a biochemical relapse (BR) after radical prostatectomy (RPE) within the first 5 years (*1*). In this case, early salvage radiation therapy (sRT) of the former prostate bed with or without androgen deprivation therapy (ADT) (*2*) is recommended. A dose-response relationship for recurrent PCa was described in several studies, suggesting that radiotherapy doses > 70 Gy should be applied to the prostatic fossa (*3*). However, the SAKK 09/10 study showed that dose escalation had a negative impact on patients' quality of life regarding urinary symptoms after sRT (*4*). Consequently, an accurate detection of the individual PCa distribution is urgently required to select suitable patients for sRT and individualize radiotherapy dose escalation within the pelvis.

In the last few years, prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) has rapidly evolved to be the gold standard in staging patients with BR: Eiber et al. reported high detection rates for PSMA PET/CT in patients with recurrent PCa, especially for patients with PSA levels of 0.5 to <1 ng/ml (73%) and 0.2 to <0.5 ng/ml (58%) (*5*). Jilg et al. proved that PSMA PET has a good sensitivity and specificity in lymph node detection for patients with BR (*6*). Keeping in mind that early salvage radiotherapy should start at PSA levels < 0.5 ng/ml, the latter observations already indicate that PSMA PET/CT can influence the decision-making process before initiation of sRT. Indeed, several studies showed that the PSMA PET/CT leads to a significant change in management of patients with BR after surgery (*7-10*).

Several studies reported their outcomes after non-PSMA PET/CT guided sRT (*11-13*) and reported biochemical control in <70% of their patients after 2 years. Zschaeck et al. performed PSMA PET-guided sRT in 22 high-risk PCa patients with BR and showed that a prolonged PSA response was achieved in hormone-naïve patients (*14*). Emmet et al. performed PSMA PET-

guided sRT in 146 patients. After a median follow-up of 10.5 months, an overall treatment response of 75% was reported (*15*).

The purpose of this German bi-institutional retrospective analysis was to assess PSA response after PSMA PET/CT-based individualization of sRT: standard radiotherapy treatment in case of BR constitutes irradiation of the prostatic fossa only. Further individualization in the sense of dose escalation to macroscopic local recurrences in the prostatic fossa and irradiation of pelvic lymphatic pathways with escalated dose to PET-positive lymph nodes and initiation of ADT was based on the findings in PSMA PET/CT. Further, biochemical recurrence free survival (BRFS) of this treatment intensified cohort was compared to historical data prior to the advent of PSMA PET/CT.

MATERIALS AND METHODS

Patient population

From February 2014 onwards, a total of 204 consecutive patients were referred for salvage radiotherapy after radical prostatectomy due to persistent or rising PSA at the departments of Radiation Oncology of the university medical centers of Munich and Freiburg. PSMA PET/CT scans were performed and patients with PSA persistence (109 patients) were excluded from this analysis as these patients are regarding tumor stage at the time of radical prostatectomy not comparable with patients with PSA decrease post-prostatectomy (*16*). Additionally, patients with PSA recurrence fare much better than patients with PSA persistence pertaining to BRFS, distant metastasis-free and overall survival (*16,17*). Five patients with first PSA recurrence after radical prostatectomy showed evidence of distant metastases on PSMA PET/CT [1/5 (20%) had non-regional lymph node metastases and 4/5 (80%) had bone metastases] and were also excluded. Thus, the following analysis is based on a cohort of 90 patients who underwent PSMA PET/CT prior to radiotherapy due to BR (Supplemental Fig. 1, Table 1). In these 90 patients, PSA

recurrence was newly diagnosed without any salvage treatment beforehand. This retrospective analysis was performed in compliance with the principles of the Declaration of Helsinki and its subsequent amendments (*18*) and was approved by the local Ethics Committee of the respective Medical Faculties (approval number of university of Freiburg 519/17; approval number of university of Munich 17-765). The requirement to obtain informed consent was waived.

Treatment application and follow up

Treatment management following PSMA PET was documented for each patient. Follow-up time was defined as the interval in months between radiotherapy and the last recorded PSA. Follow-up examination was first performed six weeks to three months after sRT and then every six to 12 months. Patients were regarded free of ADT influence after a minimum time-period of 2 months after last application of ADT.

PSMA ligand and PET/CT Imaging

PSMA-HBED-CC was radiolabelled according to good clinical practice at both medical centres as described previously (*19,20*). At the University Medical Centre Freiburg, scans were either performed with a 64-slice GEMINI TF PET/CT or a 16-slice GEMINI TF BIG BORE PET/CT (both Philips Healthcare, USA). Both scanners were cross-calibrated to ensure the comparability of the quantitative measurements. At the University Medical Center Munich, scans were either performed with a Siemens Biograph 64 or GE Discovery 690. Phantom studies based on the National Electrical Manufacturers Association NU2-2001 standard were conducted in Munich to allow for pooling of the different scanner results. At the time of the PET scan, a contrast-enhanced diagnostic CT (120 kVp, 100-400 mAs, dose modulation) or a low-dose CT (120 kVp, 25 mAs) for attenuation correction (depending on previous CT scans and contraindications) was performed. PET scans were acquired at both institutions 60 min after intravenous administration of ^{68}Ga-

PSMA (mean 205 MBq). Barring any contraindications, patients received 20mg furosemide at the time of tracer injection to avoid bladder activity.

Image interpretation

PET/CT was interpreted by one nuclear medicine physician and one radiologist or by two nuclear medicine physicians in the sense of a clinical report-based analysis. At least one of the readers had more than 5 years of PET/CT experience. Location of lesions was each determined by CT. PET-positive lesions were visually identified by ^{68}Ga-PSMA uptake above background and not associated with the physiologic uptake (*21*).

Radiotherapy Treatment

All patients received intensity-modulated radiotherapy or volumetric modulated arc therapy and image-guided radiotherapy techniques (2-5 times per week). Radiotherapy dose regimens were normo- or slightly hypo-fractionated with a boost to the PET-positive lesions applied simultaneously or sequentially. Planning CT was done in supine position. Patients were advised to have a full bladder and empty rectum. Target delineation was performed according to the Radiation Therapy Oncology Group atlas for salvage prostate cancer (*22*) and for pelvic lymph node delineation (*23*). The region of the former prostate gland is defined superiorly as 5mm above the inferior border of the vas deferens remnant, inferiorly as above the top of penile bulb, anteriorly by the pubic symphysis, posteriorly by the anterior rectum and laterally by the medial edge of the obturator internus muscle. Planning target volume was derived by expanding the CTV by a 5-7 mm margin in all directions.

Statistical analysis

BRFS (PSA ≤ 0.2 ng/ml) was defined as the study endpoint. For statistical analysis, SPSS Statistics 24 (IBM, New York, USA) was used. Time to event data was calculated using the Kaplan-Meier method. Differences between subgroups were compared using log rank test with a p value

of <0.05 considered statistically significant. Uni- and multivariate Cox-regression analyses were used to identify predictors for BRFS after PSMA PET/CT based sRT.

RESULTS

PSMA PET results

Around half of the patients (48/90; 53%) were PET-negative. If PET-positive, patients had primarily evidence of local recurrence (24/42; 27%), followed by pelvic lymph nodes (12/42; 13%) and combined local and pelvic lymph node recurrence (6/42; 7%). Median PSA at time of PET/CT for all patients was 0.43 (0.10 - 6.24). A positive PET scan was significantly ($p<0.01$ Fisher's exact test) associated with higher PSA levels: 70% of these patients had a PSA level > 0.5 ng/ml compared to patients with a negative scan with 81% of these patients having PSA levels ≤ 0.5 ng/ml (Table 1).

Management of PET-positive lesions

ADT was recommended to patients with evidence of PET-positive lesions for two years (*2*). Patients with no PET-positive findings in PET/CT were normally treated with sRT alone. Consequently, 25/42 (60%) PET-positive patients were started on ADT before initiation of sRT, 23/25 patients (92%) discontinued after a median time of 5 (2 - 23) months due to patients' preferences and 17/42 (40%) patients refused ADT altogether. One patient with no PET-positive findings received ADT concomitantly with radiotherapy and thereafter due to a Gleason score of 9 and p-stage T3b. In all but one patient, the prostatic fossa was irradiated with a median total dose of 66 Gy in 2.0 Gy (59.4 - 70.2 Gy). In case of PET-positive pelvic lymph nodes, pelvic lymphatic pathways were treated with a normo-fractionated overall dose of 45 - 50.4 Gy. At the discretion of the treating physician, the boost to the PET-positive lymph nodes was either delivered simultaneously (15/18 (83%); 54 - 61.6 Gy in 1.9 - 2.4 Gy) or sequentially (3/18 (17%); 9 - 12.6 Gy in 1.8 Gy). Likewise, a simultaneous integrated (13/30 (43%); 70.2 Gy in 2.1 - 2.4 Gy) or

sequential boost (17/30 (57%); 3.8 - 25.2 Gy in 1.8 Gy) was applied in case of local recurrence on PET/CT. The aforementioned patient omitted from irradiation delivered to the prostatic fossa had a low risk of local recurrence and a singular internal iliac lymph node metastasis on PET/CT. He received irradiation of the pelvic lymphatic pathways only with simultaneous integrated boost to the PET-positive lymph node metastasis. Treatment characteristics are listed in Table 2.

Patients' outcome

Median follow-up was 23 months (1 - 47). Median post-sRT PSA nadir was 0.07 ng/ml (<0.03 - 1.18) with 69/90 patients (77%) presenting with a PSA ≤ 0.1 ng/ml and 73/90 (81%) with a PSA ≤ 0.2 ng/ml. The median and mean time between end of radiotherapy and PSA nadir were 3 and 4.89 months (1 - 21 months), respectively. At time of PSA nadir measurement, 13/90 patients (14%) had ongoing ADT and 6/90 patients (7%) were still under the influence of ADT. At last follow-up, median PSA was 0.07 ng/ml (<0.03 - 4.92) with 78% of all patients having a PSA ≤ 0.2 ng/ml (Fig. 1). 23/26 patients (88%) with concomitant ADT discontinued ADT after sRT: median time between last application of ADT and last PSA measurement was 19 months (range 2-36). 69/87 patients (80%) without ADT at last follow-up had a PSA ≤ 0.2 ng/ml at last contact. No significant difference in patients with or without PET-positive findings prior to sRT regarding BRFS was observed at last follow-up (78% vs. 82%; p= 0.392; Fig. 2). Additionally, the usage of ADT had neither in PET-positive nor in PET-negative patients an influence on BRFS at last follow-up (p= 0.410; Fig. 3). Patients' outcome after sRT is summarized in Table 3.

Factors predicting PSA response at last follow-up

Uni- and multivariate analysis was conducted to assess whether there was an association between BRFS and tumour or treatment specific variables (Supplemental Table 1) and PSMA PET/CT imaging results. A post-radiotherapy PSA nadir ≤ 0.1 ng/ml was an independent factor for BRFS irrespective of ongoing ADT. All the other factors had no significant impact on BRFS.

Toxicity

Acute genitourinary and gastrointestinal toxicity grade 2 according to common terminology criteria for adverse events (CTCAE) v.4.03 was observed in 12/90 patients (13%) and 14/90 patients (16%). Late genitourinary and gastrointestinal toxicity grade 2 was seen in 12/90 patients (13%) and 3/90 patients (3%), respectively. There were 2 patients with late genitourinary toxicity grade 3 – one with a radiation or non-infectious cystitis and the other with urinary incontinence. There was no patient with grade 4 or 5 toxicity (Supplemental Table 2).

DISCUSSION

The main aim of this study was to assess whether the excellent results of PSMA PET/CT in the detection of recurrent PCa after RPE translates into improved BRFS for patients treated with PSMA PET-guided sRT.

As already extensively studied (*10,24,25*), PSMA PET/CT leads to remarkable treatment adaptation. In 42/90 patients (47%) PET-positive recurrent disease was detected, hence triggering dose-escalation, enlargement of radiotherapy volumes and initiation of ADT.

Based on a median follow-up of 23 months, our analysis shows that there is a high rate and long-lasting treatment response to irradiation based on pre-treatment PSMA PET/CT with an overall low toxicity profile. At last follow-up, 78% of patients had a PSA ≤ 0.2 ng/ml. When restricting the analysis to patients without ADT at last follow-up, the benefit of PSMA PET/CT-based sRT becomes even more evident: 80% with a PSA ≤ 0.2 ng/ml.

Numerous studies reported on outcome after non-PSMA PET/CT based sRT with a varying proportion of patients with accompanying ADT, pelvic lymphatic pathways irradiation and differing pre-sRT PSA levels (Table 4) (*2,12,13,26-29*). In comparison to studies in the pre-PSMA PET/CT era, our results on BRFS after a median time of 23 months were favorable. Seemingly, the

individualized intensification of treatment, exclusion of patients with distant metastases as well as the early initiation of salvage radiotherapy at a median PSA of 0.44 ng/ml explain these findings. Furthermore, this mirrors recent recommendations by the American Society for Radiation Oncology to start with sRT as early as possible (*30*). Our observations are largely in accordance with the limited number of analyses on outcome after PSMA PET/CT-based sRT in recurrent PCa with mostly shorter follow-up (*14,15,31*). Zschaeck et al. (*14*) reported on PSMA-based sRT of 20 recurrent high-risk PCa patients. After a median follow-up of 29 months, median PSA was 0.15 ng/ml. This corresponds well to the median PSA of 0.07 ng/ml after 23 months in our cohort. Besides, Emmett et al. (*15*) reported on treatment outcome after PSMA PET-based radiotherapy with a shorter median follow-up of 10.5 months and observed an overall treatment response of 72% (71/99 patients). This is lower than the treatment response in our analysis most likely due to their inclusion of patients with metastatic disease beyond nodal involvement within the pelvis and possibly of patients with persistent post-prostatectomy PSA, although this is not clearly stated. The authors reported that nodal involvement in PSMA PET had a negative influence on BRFS compared to patients with no PET findings or PET-positive lesions restricted to the fossa. In our analysis, neither PET-positive lesions in general nor PET-positive lymph nodes had an impact on BRFS. At initial observation, this result is surprising, as one would assume that patients with visible recurrent disease would have a worse BRFS. Firstly, it is not clearly stated, whether the patients analyzed by Emmett et al. received irradiation of PET-positive lymph nodes only or of the surrounding lymphatic pathways as well, as it was the case with our patients. Secondly, contrary to Emmett et al., we did not exclude patients who received ADT concomitantly with radiotherapy. Thus, treatment-intensification in patients with PET-positive findings could have led to a similar BRFS between patients with a negative PET-scan vs. local vs. lymph node recurrence. Previously, Jilg et al. observed a high microscopic tumor spread in the surrounding lymphatic tissue of PSMA PET-positive nodes (*6*). Thus, contrary to the “Pokemet” approach to metastatic PCa (*32*), we do not believe in stereotactic body radiotherapy of PET-positive nodes only but in eradicating

microscopic spread to surrounding lymphatic pathways, dose-escalation to macroscopic tumor burden and at least concomitant use of ADT.

Nevertheless, 18% of the patients with PET-negative findings had a PSA > 0.2 ng/ml at last follow-up. PSMA PET/CT may still underestimate the true extent of disease for detection of small volume lymph nodes (*33,34*). In our opinion, PSMA PET/CT should therefore not result in an omission of nomogram (*35*) triggered radiotherapy treatment volumes.

In our cohort, a significant correlation between a post-radiotherapy PSA nadir ≤ 0.1 ng/ml and a PSA ≤ 0.2 ng/ml at last follow-up was present. This mirrors recent data by Bartkowiak et al. (*36*) demonstrating that men with undetectable post-radiotherapy PSA have lower rates of metastases and a better overall survival. Previous data demonstrated a strong dependence of progression-free survival on pre-salvage radiotherapy PSA (*36,37*). The analyses of Tendulkar et al. and Bartkowiak et al. (*36,37*) in this regard incorporated patients of the pre-PSMA PET era and sRT approach was not based on advanced imaging that would allow for adaptation of treatment like dose escalation to the macroscopic tumor recurrence and exclusion of metastatic disease. Most likely, this explains why there was no such dependence of BRFS on the pre-salvage radiotherapy PSA in the present cohort, as patients with a higher pre-salvage radiotherapy PSA and thus in most cases with evidence of locoregional pelvic recurrence received an individualized, escalated sRT based on the PSMA PET/CT results.

Our study has several limitations mainly due to its retrospective character: the treatment protocols and the follow-up procedure were not identical for all patients. Another issue is the radiation dose applied to PET-positive lesions in the prostatic fossa and to PET-positive pelvic lymph nodes: Zilli et al. (*11*) delivered 74 Gy to MRI-positive local relapses and D'Angellilo et al. (*38*) delivered up to 80 Gy to choline PET-positive lesions in the prostatic fossa. In comparison, dose escalation to macroscopic local recurrences in our study was performed with an overall lower dose up to 72 Gy. Thus, future studies should aim to assess the optimal sRT dose for PET-positive

regions and clarify whether higher radiotherapy doses to PET-positive regions may enable deferral of ADT. Further shortcomings of the present analysis that limit final conclusions are the relatively short follow-up due to the only recent availability of PSMA PET/CT and differing duration of ADT in 26/90 patients (29%), but with most patients (88%) discontinuing ADT after 5 months and relatively long before last PSA measurement. Hence, at best our primary endpoint, BRFS, may serve as a surrogate marker for PCa-specific survival or overall survival.

CONCLUSION

We observed a 78% BRFS rate after PSMA PET/CT-guided salvage radiotherapy and no differences in BRFS between patients with PET-positive and PET-negative lesions, indicating effective targeting of PET-positive lesions. To confirm the observed outcome improvement by PSMA PET/CT-guidance, a prospective observational study at both institutions is in planning.

DISCLOSURE

Conflict of Interest: The authors declare that they have no conflict of interest.

REFERENCES

1. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. *J Urol.* 2003;169:517-523.

2. Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. *New Engl J Med.* 2017;376:417-428.

3. King CR. The dose-response of salvage radiotherapy following radical prostatectomy: A systematic review and meta-analysis. *Radiother Oncol.* 2016;121:199-203.

4. Ghadjar P, Hayoz S, Bernhard J, et al. Acute toxicity and quality of life after dose-intensified salvage radiation therapy for biochemically recurrent prostate cancer after prostatectomy: first results of the randomized trial SAKK 09/10. *J Clin Oncol.* 2015;33:4158-4166.

5. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid (68)Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical rrostatectomy. *J Nucl Med.* 2015;56:668-674.

6. Jilg CA, Drendel V, Rischke HC, et al. Diagnostic accuracy of Ga-68-HBED-CC-PSMA-ligand-PET/CT before salvage lymph node dissection for recurrent prostate cancer. *Theranostics.* 2017;7:1770-1780.

7. Calais J, Czernin J, Cao M, et al. (68)Ga-PSMA PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA<1.0ng/ml: Impact on salvage radiotherapy planning. *J Nucl Med.* 2018;59:230-237.

8. Roach PJ, Francis R, Emmett L, et al. The impact of (68)Ga-PSMA PET/CT on management intent in prostate cancer: results of an Australian prospective multicenter study. *J Nucl Med.* 2018;59:82-88.

9. Hope TA, Aggarwal R, Chee B, et al. Impact of 68Ga-PSMA-11 PET on management in patients with biochemically recurrent prostate cancer. *J Nucl Med.* 2017;58:1956-1961.

10. Calais J, Fendler WP, Eiber M, et al. Actual impact of 68Ga-PSMA-11 PET/CT on the management of prostate cancer patients with biochemical recurrence. *J Nucl Med.* 2018;59:434-441.

11. Zilli T, Jorcano S, Peguret N, et al. Results of dose-adapted salvage radiotherapy after radical prostatectomy based on an endorectal MRI target definition model. *Am J Clin Oncol.* 2017;40:194-199.

12. Goenka A, Magsanoc JM, Pei X, et al. Long-term outcomes after high-dose postprostatectomy salvage radiation treatment. *Int J Radiat Oncol Biol Phys* 2012;84:112-118.

13. Ervandian M, Høyer M, Petersen SE, et al. Salvage radiation therapy following radical prostatectomy. A national Danish study. *Acta Oncol.* 2016;55:598-603.

14. Zschaeck S, Wust P, Beck M, et al. Intermediate-term outcome after PSMA-PET guided high-dose radiotherapy of recurrent high-risk prostate cancer patients. *Radiat Oncol.* 2017;12:140.

15. Emmett L, Van Leeuwen P, Nandurkar R, et al. Treatment outcomes from (68)GaPSMA PET CT informed salvage radiation treatment in men with rising PSA following radical prostatectomy: Prognostic value of a negative PSMA PET. *J Nucl Med.* 2017;58:1972-1976.

16. Wiegel T, Bartkowiak D, Bottke D, et al. Prostate-specific antigen persistence after radical prostatectomy as a predictive factor of clinical relapse-free survival and overall survival: 10-year data of the ARO 96-02 trial. *Int J Radiat Oncol Biol Phys.* 2015;91:288-294.

17. Bianchi L, Nini A, Bianchi M, et al. The role of prostate-specific antigen persistence after radical prostatectomy for the prediction of clinical progression and cancer-specific mortality in node-positive prostate cancer patients. *Eur Urol.* 2016;69:1142-1148.

18. Association GAotWM. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Am Coll Dent.* 2014;81:14-18.

19. Weineisen M, Simecek J, Schottelius M, Schwaiger M, Wester H-J. Synthesis and preclinical evaluation of DOTAGA-conjugated PSMA ligands for functional imaging and endoradiotherapy of prostate cancer. *Eur J Nucl Med Mol Imaging.* 2014;4:1-15.

20. Zamboglou C, Wieser G, Hennies S, et al. MRI versus 68Ga-PSMA PET/CT for gross tumour volume delineation in radiation treatment planning of primary prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43:889-897.

21. Fendler WP, Eiber M, Beheshti M, et al. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. *Eur J Nucl Med Mol Imaging.* 2017;44:1014-1024.

22. https://www.rtog.org/CoreLab/ContouringAtlases/ProstatePostOp.aspx. Accessed on 01.29.2018.

23. Lawton CAF, Michalski J, El-Naqa I, et al. RTOG GU Radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;74:383-387.

24. Albisinni S, Artigas C, Aoun F, et al. Clinical impact of (68) Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) in patients with prostate cancer with rising prostate-specific antigen after treatment with curative intent: preliminary analysis of a multidisciplinary approach. *BJU Int.* 2017;120:197-203.

25. Bluemel C, Linke F, Herrmann K, et al. Impact of 68Ga-PSMA PET/CT on salvage radiotherapy planning in patients with prostate cancer and persisting PSA values or biochemical relapse after prostatectomy. *Eur J Nucl Med Mol Imaging Research.* 2016;6:78.

26. Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA.* 2004;291:1325-1332.

27. Stish BJ, Pisansky TM, Harmsen WS, et al. Improved metastasis-free and survival outcomes with early salvage radiotherapy in men With detectable prostate-specific antigen after prostatectomy for prostate cancer. *J Clin Oncol.* 2016;34:3864-3871.

28. Miyake M, Tanaka N, Asakawa I, et al. Proposed salvage treatment strategy for biochemical failure after radical prostatectomy in patients with prostate cancer: a retrospective study. *Radiat Oncol.* 2014;9:208.

29. Abugharib A, Jackson WC, Tumati V, et al. Very early salvage radiotherapy improves distant metastasis-free survival. *J Urol.* 2017;197:662-668.

30. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. *J Urol.* 2013;190:441-449.

31. Henkenberens C, Von Klot CA, Ross TL, et al. 68Ga-PSMA Ligand PET/CT-based radiotherapy for lymph node relapse of prostate cancer after primary therapy delays initiation of systemic therapy. *Anticancer Res.* 2017;37:1273-1279.

32. Murphy DG, Sweeney CJ, Tombal B. “Gotta Catch 'em All”, or Do We? "Pokemet" Approach to Metastatic Prostate Cancer. *Eur Urol.* 2017;72:1-3.

33. Maurer T, Gschwend JE, Rauscher I, et al. Diagnostic efficacy of (68)Gallium-PSMA Positron Emission Tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. *J Urol.* 2016;195:1436-1443.

34. van Leeuwen PJ, Emmett L, Ho B, et al. Prospective evaluation of 68Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer. *BJU Int.* 2017;119:209-215.

35. Wu R, Woodford H, Capp A, et al. A prospective study of nomogram-based adaptation of prostate radiotherapy target volumes. *Radiat Oncol.* 2015;10:243.

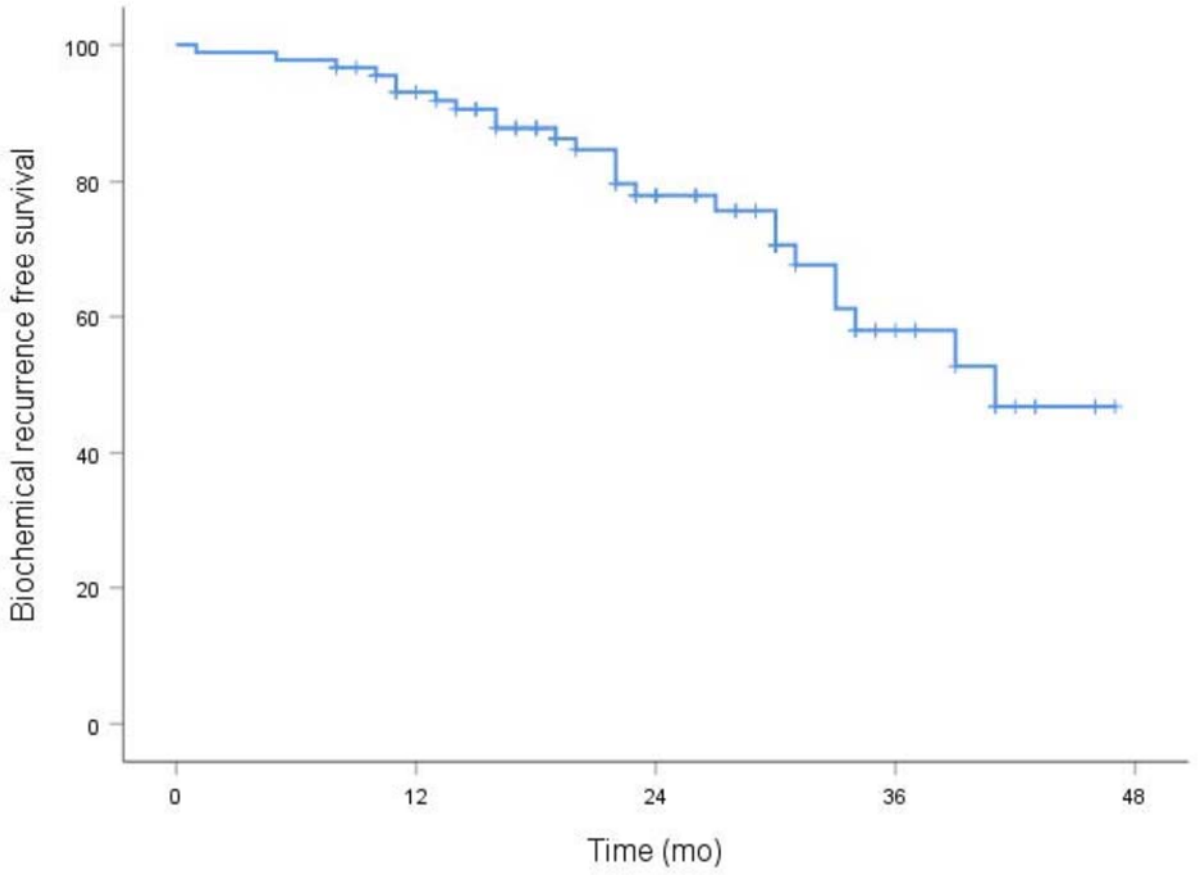
36. Bartkowiak D, Thamm R, Bottke D, et al. Prostate-specific antigen after salvage radiotherapy for postprostatectomy biochemical recurrence predicts long-term outcome including overall survival. *Acta Oncol.* 2017:1-6.

37. Tendulkar RD, Agrawal S, Gao T, et al. Contemporary update of a multi-institutional predictive nomogram for salvage radiotherapy after radical prostatectomy. *J Clin Oncol.* 2016;34:3648-3654.

38. D'Angelillo RM, Sciuto R, Ramella S, et al. 18F-Choline positron emission tomography/computed tomography–driven high-dose salvage radiation therapy in patients with biochemical progression after radical prostatectomy: Feasibility study in 60 Patients. *Int J Radiat Oncol Biol Phys.*90:296-302.

FIGURES

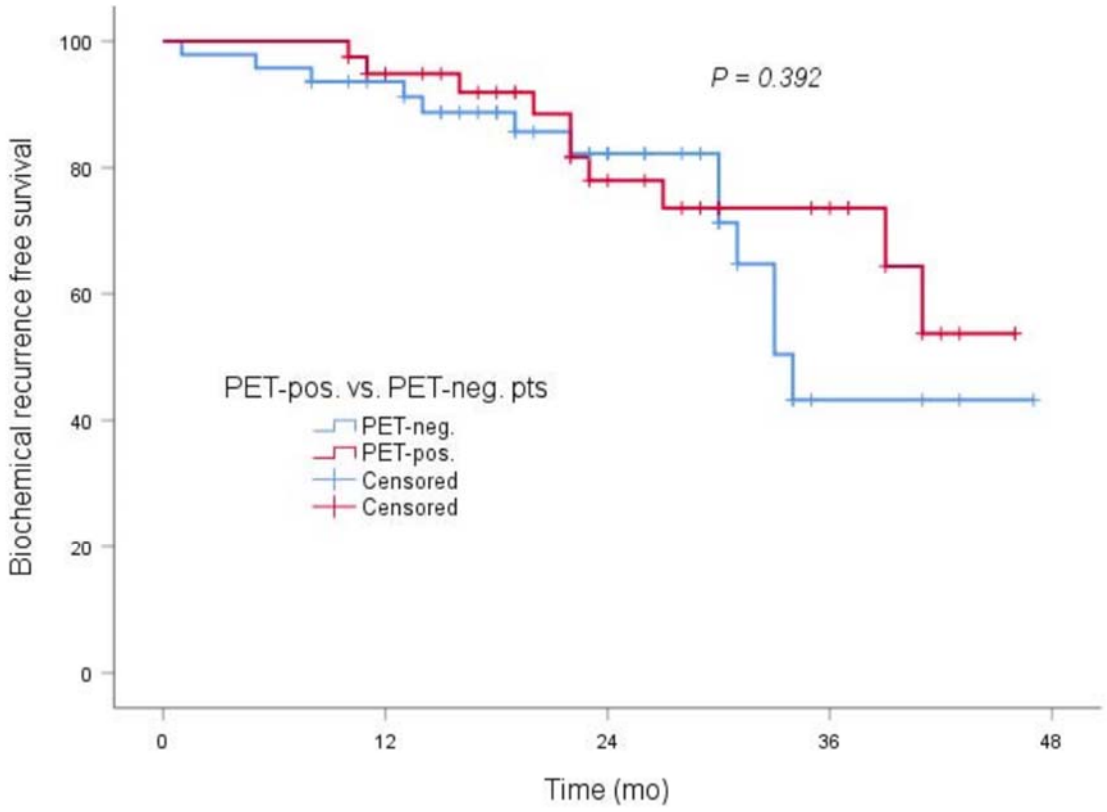
Fig. 1



Number at risk	90	74	41	14	0
Number on ADT	26	6	2	-	-

Biochemical recurrence-free survival (≤0.2 ng/ml) in all patients at last follow-up

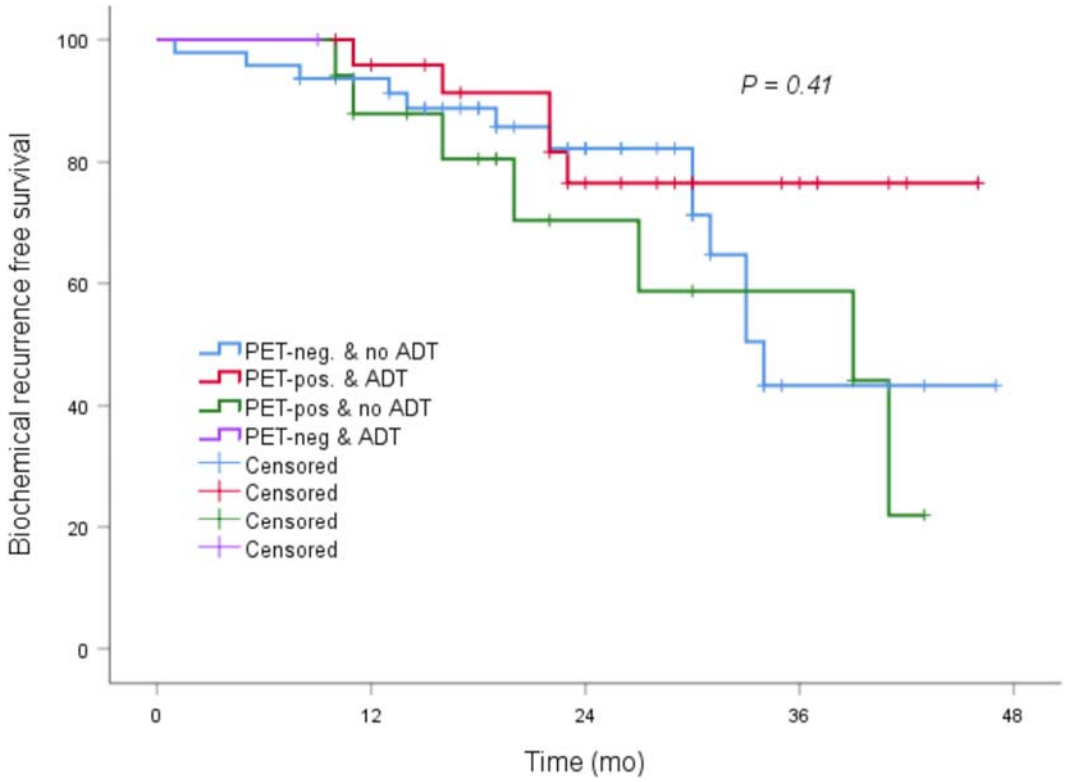
Fig. 2



Number at risk	PET-pos.	40	28	16	4	0
	ADT	25	6	2	-	-
	PET-neg.	47	39	23	3	0
	ADT	1	0	0	0	0

Biochemical recurrence-free survival (≤0.2 ng/ml) in all patients without antiandrogen therapy at last follow-up (PET-positive vs. PET-negative)

Fig. 3



Number at risk	PET neg. & no ADT	47	39	19	3	0
	PET pos. & ADT	25	22	13	6	0
	PET pos. & no ADT	17	13	6	4	0
	PET. neg. & ADT	1	1	0	0	0
	Number of pts on ADT	26	6	2	-	-

Biochemical recurrence-free survival (≤0.2 ng/ml) in PET-positive vs. PET-negative patients with/without concomitant ADT

TABLES

Table 1: Patients' characteristics**.**

	All patients
N	90
Median age	73
Tumor stage	
pT2a/b	10 (11%)
pT2c	44 (49%)
pT3a	23 (26%)
pT3b	11 (12%)
pT4	2 (2%)
Nodal stage	
pN0	66 (73%)
pN1	11 (12%)
pNx/cN0	13 (15%)
Positive surgical margins	28 (31%)
Gleason score	
6	8 (9%)
7a	25 (27%)
7b	33 (37%)
8	15 (17%)
9	9 (10%)
Median PSA at RPE	8.55 (2.37 - 48.0)
Postoperative PSA	0.03 (0.0 - 0.19)
Months since RPE until PSA recurrence (mean)	62 (8 - 199)
Median PSA at PSMA PET/CT	0.43 (0.10 - 6.24)
Median PSA at PSMA PET/CT in PET-positive pts (n= 42)	0.78 (0.23 - 6.24)
Median PSA at PSMA PET/CT in PET-negative pts (n= 48)	0.30 (0.1 - 3.24)
PSMA PET/CT result	
Negative	48 (53%)
Fossa recurrence only	24 (27%)
Lymph node positive only	12 (13%)
Fossa and lymph node recurrence	6 (7%)

Table 2: Treatment characteristics

	All patients	**PET-positive**	**PET-negative**
	90	42	48
ADT			
ADT with stop before last follow up / duration (months)	23 / 5 (2 - 23)	23 / 5 (2 – 23)	-
Ongoing ADT at last follow up	3	2	1
No ADT	64	17	47
Median PSA before RT	0.44 (0.11 - 6.24)	0.68 (0.3 - 6.24)	0.34 (0.11 - 3.24)
RT			
Former Prostate	66 Gy (59.4 - 70.2 Gy)		
Lymphatic pathways	50.4 Gy (45 - 50.4)		
PET-pos. local recurrence	70.0 Gy (67.2 - 72 Gy)		
PET-pos. LN	60.76 Gy (54 - 66)		
RT technique			
VMAT/IMRT & IGRT	All pts		

ADT = androgen deprivation therapy, RT = radiation therapy, VMAT = volumetric modulated arc therapy, IMRT = intensity modulated radiotherapy, IGRT = image guided radiotherapy

Table 3: Outcome after salvage radiotherapy

	All patients	**PET-positive**	**PET-negative**
	90	42	48
Median Follow-up (months)	23 (1 - 47)		
PSA at last follow-up	**n= 90**	**n= 42**	**n= 48**
Median PSA	0.07 (<0.03 - 4.92)	0.07 (<0.03 - 4.92)	0.07 (0.01 - 1.3)
PSA ≤ 0.1 ng/ml	78%	74%	82% p= 0.377
PSA ≤ 0.2 ng/ml	78%	74%	82% p= 0.662
PSA at last follow-up without ADT	**n= 87**	**n= 40**	**n= 47**
Median PSA	0.07 (<0.03 - 4.92)	0.07 (<0.03 - 4.92)	0.07 (<0.03 - 1.3)
PSA ≤ 0.1 ng/ml	80%	78%	82% p= 0.191
PSA ≤ 0.2 ng/ml	80%	78%	82% p= 0.392
Clinical Progress			
Distant Metastases	None		
Death	None		

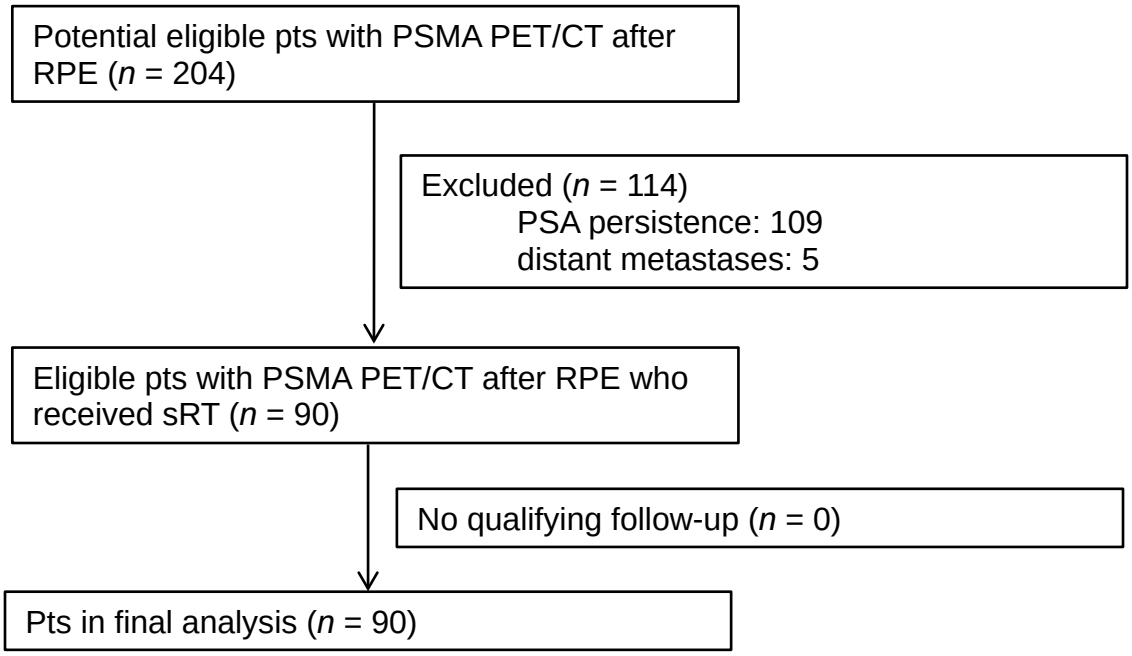
ADT = androgen deprivation therapy

Table 4: Comparison between PSMA PET-guided sRT with non-image guided sRT studies

Study	No. of patients	Median sRT dose to fossa (range)	sRT to pelvic lymph nodes (% of patients)	Median PSA pre-sRT (ng/ml)	% of patients with ADT	Guided by PSMA PET/CT	BRFS at 2 years
Stephenson et al.	501	64.8 (<59.4 - >70) Gy	yes (5)	0.72	17	no	<60%
Ervandian et al.	259	69 (66 - 74) Gy	no	n/a	40.3	no	<70%
Goenka et al.	285	n/a (<70 - ≥70) Gy	yes (7)	0.4	31	no	<65%
Stish et al.	1106	68 (64.8 - 70.2) Gy	yes (4)	0.6	16.3	no	<70%
Miyake et al.	61	70 Gy	yes (n/a)	0.56	35.1	no	55%
Abugharib et al.	657	68 (59.4 - 72) Gy	yes (n/a)	0.4	24	no	<70%
Shipley et al. (*study arm without ADT)	376	64.8 Gy	no	0.6	0*	no	80%
Our study	90	66 (59.4 - 70.2) Gy to the fossa / 70 (67.2 - 72) Gy to local recurrences	yes (20)	0.44	27.8	yes	78%

Please note that Shipley et al. (PSA nadir after sRT + 0.3 ng/ml) and Stephenson et al. (PSA nadir after sRT + 0.1 ng/ml or continuous PSA increase) had to our study different definitions of BRFS. sRT= salvage radiotherapy, ADT = androgen deprivation therapy, BRFS = biochemical recurrence free survival, n/a = not available

Supplemental Fig. 1



Flow chart (modified from the CONSORT 2010 Flow diagram).

Abbreviations: pts = patients, RPE = radical prostatectomy.

Supplemental Table 1: Uni- and multivariate Cox-Regression analyses considering biochemical recurrent free survival

	Univariate analysis	**Multivariate analysis***	
	p value	p value	HR (95% CI)
initial PSA in ng/ml (<10, 10-20, >20)	0.779	0.808	1.08 (0.58-2)
Gleason Score (<7, 7, >7)	0.485	0.726	1.15 (0.53-2.48)
pT (2a, 2b+2c, 3)	0.953	0.844	0.92 (0.38-2.19)
pN (0,1)	0.346	0.529	0.81 (0.42-1.57)
Surgical margins (0,1)	0.204	0.858	1.13 (0.3-4.2)
PSA pre sRT in ng/ml (<0.5, ≥0.5)	0.707	0.215	1.85 (0.7-4.89)
PET findings (negative, fossa, lymph nodes ± fossa)	0.697	0.738	1.12 (0.57-2.24)
Dose escalation prostate fossa (≤66.6Gy, >66Gy	0.601	0.951	0.97 (0.34-2.79)
Dose escalation pelvic lymph nodes (≤50.4Gy, >50.4Gy)	0.738	0.834	0.95 (0.43-1.87)
ADT during sRT (negative, positive)	0.164	0.404	2 (0.39-10.24)
PSA nadir ≤ 0.1ng/ml	**<0.001**	**0.006**	**0.04 (0.004-0.4)**

*****Multivariate analysis was performed including all parameters in all patients. Additionally multivariate analyses was performed including only patient related parameters (PSA, Gleason score, pT stage, pN stage, surgical margins and PET findings) and treatment related parameters (dose escalation to fossa and lymph nodes, ADT) in all patients: none of the parameters was significant (data not shown). Additionally, the multivariate analysis was repeated due to possible confounding bias in patients without ADT (86 patients) and similar results as for the whole collective were observed (data not shown). Bold: significant parameters. Abbrevations: HR = hazard ratio, CI = confidence interval

Supplemental Table 2: Acute and late toxicity according to common terminology criteria for adverse events (CTCAE) v.4.03

	Acute toxicity			**Late toxicity**		
	n and (%) of pts by grade			**n and (%) of pts by grade**		
	1	**2**	**3**	**1**	**2**	**3**
Bladder	39 (43%)	12 (13%)	-	18 (20%)	12 (13%)	2 (2%)
Bowel	33 (37%)	14 (16%)	-	6 (7%)	3 (3%)	-
Skin	3 (3%)	-	-	-	-	-