

# The maximum standardized uptake value in patients with recurrent or persistent prostate cancer after radical prostatectomy and PSMA-PET-guided salvage radiotherapy—a multicenter retrospective analysis

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# Abstract

## Purpose:

This study aims to evaluate the association of the maximum standardized uptake value (SUVmax) in positron-emission tomography targeting prostate-specific-membrane-antigen (PSMA-PET) prior to salvage radiotherapy (sRT) on biochemical recurrence free survival (BRFS) in a large multicenter cohort.

## Methods:

Patients who underwent  $^{68}\text{Ga}$ -PSMA11-PET prior to sRT were enrolled in four high-volume centers in this retrospective multicenter study. Only patients with PET-positive local recurrence (LR) and/or nodal recurrence (NR) within the pelvis were included. Patients were treated with intensity-modulated-sRT to the prostatic fossa and elective lymphatics in case of nodal disease. Dose escalation was delivered to PET-positive LR and NR. Androgen deprivation therapy was administered at the discretion of the treating physician. LR and NR were manually delineated using and SUVmax was extracted for LR and NR. Cox-regression was performed to analyze the impact of clinical parameters and the SUVmax-derived values on BRFS.

## Results:

235 patients with a median follow up (FU) of 24 months were included in the final cohort. 2-years and 4-years BRFS for all patients were 68% and 56%. The presence of LR was associated with favorable BRFS ( $p = 0.016$ ). Presence of NR was associated with unfavorable BRFS ( $p = 0.007$ ). While there was a trend for SUVmax values  $\geq$  median ( $p = 0.071$ ), SUVmax values  $\geq$  75%quartile in LR were significantly associated with unfavorable BRFS ( $p = 0.022$ , HR: 2.1, 95%CI 1.1–4.6). SUVmax value in NR was not significantly associated with BRFS. SUVmax in LR stayed significant in multivariate analysis ( $p = 0.030$ ). Sensitivity analysis with patients for who had a FU of  $> 12$  months ( $n = 197$ ) and only LR confirmed these results.

## Conclusion

The non-invasive biomarker SUVmax can prognosticate outcome in patients undergoing sRT and recurrence confined to the prostatic fossa in PSMA-PET. Its addition might contribute to improve risk-stratification of patients with recurrent PCa and to guide personalized treatment decisions in terms of treatment intensity adaption.

## Introduction

Up to 50% of patients with localized prostate cancer (PCa) undergoing radical prostatectomy (RP) experience biochemical relapse within the first five years after treatment <sup>1-3</sup>. Early salvage radiation therapy (sRT) with or without androgen deprivation therapy (ADT) is recommended as the only curative treatment option <sup>4</sup>. However, recurrence rate after sRT is represented by heterogeneous patterns and influenced by clinico-pathological features such as pre-treatment prostate-specific antigen values (PSA), International Society of Urological Pathology Grade (ISUP), extracapsular extension (ECE), seminal vesicle infiltration (SVI) and surgical margins with progression-free survival rates vary between 20% and 70% after 5 years <sup>2,5</sup>. Therefore, additional prognostic markers are needed to

improve risk stratification and guide personalized treatment approaches such as dose escalation, adaption of RT fields or intensification of systemic treatments. Implementation of positron emission tomography (PET) targeting the prostate-specific-membrane-antigen (PSMA), a cell-surface transmembrane protein over-expressed in PCa cells<sup>6</sup>, as it improves detection rates of recurrent PCa lesions even at low PSA levels and outside the prostatic fossa<sup>7,8</sup>. These findings have high impact on the management of salvage treatments with alteration in approximately half of patients<sup>9–11</sup>. Whilst retrospective evidence supports putative improvements of biochemical recurrence free survival rates due to PSMA-PET guided sRT<sup>12,13</sup>, results of prospective trials are pending (<sup>14</sup>, NCT04794777, PATRON–NCT04557501). Emerging data suggest, that the maximum standardized uptake value (SUVmax) can be used as a biomarker to prognosticate clinically significant PCa<sup>15</sup>, Gleason-Score (GS)<sup>16,17</sup> and distant metastases<sup>18</sup> in primary PCa, but no data exist on the applicability of this PSMA-PET feature in patients with relapse undergoing sRT. In search of new, non-invasive biomarkers for personalized risk stratification, this retrospective multicenter study aims to evaluate the impact of the SUVmax on biochemical recurrence free survival (BRFS) in patients with recurrent or persistent PCa cancer after RP and <sup>68</sup>Ga-PSMA11-guided salvage radiotherapy.

## Methods

### Patients and treatment

This multicenter study collected from high-volume centers in Germany (University Medical Centre Freiburg, Klinikum Rechts der Isar Technical University Munich (TUM), University Hospital of the Ludwig-Maximilian-University Munich (LMU)) and Italy (IRCCS Azienda Ospedaliero-Universitaria di Bologna). The study received institutional review board approval from all participating institutions (Freiburg No.: 15/18; TUM:466/16 S; Bologna: 385/2021/Oss/AOUBo, LMU: 17–765). The centers collected data from patients who received radical surgery. and underwent <sup>68</sup>Ga-PSMA11-PET due to PSA persistence (PSA after surgery  $\geq 0.1$  ng/ml) or recurrence (PSA  $\geq 0.2$  as nadir after surgery) and were subsequently treated with PSMA-PET-guided sRT. Treatment decisions were taken locally at the discretion of the treating physicians according to standards of care at the time of treatment<sup>4</sup> and based on PSMA-PET/CT findings. See supplementary Table 1 for details on salvage RT concepts. ADT was administered at the discretion of the treating physician. Patients were excluded if distant metastases (DM, lymph nodes above the iliac bifurcation, bone metastases or visceral metastases) were present in PSMA PET/CT and if ADT was given prior to PSMA PET/CT scans. 251 patients with local recurrence (LR) and/or nodal recurrence (NR) treated with sRT between 2014 and 2020 met initial inclusion criteria. 16 patients were excluded due to equivocal PET findings not suitable for accurate contouring of PET-lesions, resulting in 235 patients in the final cohort. Additionally, a subgroup of patients with Follow-Up time > 12 months was created (n = 197). See Fig. 1 for a consort flow diagram.

#### <sup>68</sup>Ga-PSMA11 PET and images analysis

<sup>68</sup>Ga-PSMA11 was synthesized according to good manufacture practice in all centers and in accordance with International procedural guidelines<sup>19</sup>. PET/CT images were acquired approximately 60 min after tracer injection (approximately 1.8–2.2 MBq <sup>68</sup>Ga-PSMA11 per kg bodyweight) in all centers and for the PSMA PET/CT contrast-enhanced or unenhanced CTs using a slice thickness of 2mm 120 kVp, 100–400 mAs, dose modulation) were performed for attenuation correction. The following scanners were used: Freiburg: 16-slice Gemini TF Big Bore, 64-slice Gemini TF or Vereos, all Philips Healthcare, USA; TUM: Biograph mCT/128 slice CT, Siemens Healthineers, Germany; LMU: Biograph 64 (Siemens Healthineers, Germany) or Discovery 690 /GE Healthcare, USA; Bologna:

Discovery STE or Discovery 710, both GE Healthcare, USA). All scanners fulfilled the requirements indicated in the European Association of Nuclear Medicine (EANM) imaging guidelines and obtained EANM Research Ltd. (EARL) accreditation during acquisition. All systems resulted in a PET image with a voxel size of  $2 \times 2 \times 2 \text{ mm}^3$ . Images were normalized to decay corrected injected activity per kg body weight (SUV g/ml).

All PSMA-PET images were locally reviewed prior to data sharing by two nuclear medicine physicians with experience on PCa imaging and according to reporting international guidelines<sup>20,21</sup>. Disagreements were resolved by consensus.

## Image processing

Image analysis was performed with 3D Slicer v4.10.0<sup>22</sup>. Considering the local nuclear medicine report, PSMA-PET positive LR and NR lesions were manually contoured by one reader (SS) with > 3 years' experience in PSMA-PET segmentation using a window level from SUVmin-max:0–5 based on previous windowing recommendations in primary PCa patients<sup>23</sup>. Under consideration of CT images and available PSMA-PET/CT results any focal uptake higher than adjacent background in more than one slice was considered to represent PCa. Equivocal or small findings limited to one slice were not segmented. SUVmax was extracted for each lesion separately. Since segmentation of LR adjacent to the bladder wall can be challenging an inter-observer variability analysis was performed by a second experienced reader (CZ) in a subset of 15 cases.

## Data collection and Follow-Up

Data collection included age at sRT, International Society of Urologic Pathology Grading (ISUP), pathological T, N-stage and status of surgical margins after RPE, PSA prior to sRT, site of recurrence (local, nodal or both), administration and duration of ADT and sRT doses. Follow-up assessments included serum PSA testing at regular intervals based on the institutional clinical praxis.

## Statistical analysis

The primary study endpoint was BRFS, defined as serum PSA > 0.2 ng/ml above the post-sRT nadir without initiation of additional salvage therapies or death of any cause. Descriptive statistics were performed with Excel 2016 (Microsoft Cooperation, USA) and Graph Pad Prism v8.4.2 (GraphPad Software Inc, USA). Uni- and multivariate Cox-regression was performed with SPSS v27.0 (IBM, USA) to assess the impact of the different variables on BRFS.

Variables were dichotomized: ISUP < 3 and  $\geq 3$ , pathological T stage < pT3 and  $\geq$  pT3, pathological N stage pN+ and pN-, positive surgical margin vs negative surgical margin, pre-sRT PSA < 0.5ng/ml and > 0.5ng/ml, presence and absence of local recurrence, presence and absence of nodal recurrence, administration or omission of ADT. Due to missing established threshold values, SUVmax values dichotomized < median and  $\geq$  median as well as < 75%quartile (third quartile) and  $\geq$  75%quartile of the values of the cohort. Kaplan-Meier survival curves compared by log-rank test (Graph Pad Prism v8.4.2, GraphPad Software Inc, USA) were used for analysis of the respective parameters. Thresholds of median and 75% quartile SUVmax values were applied separately for LR and NR lesions. The respective threshold of the whole cohort was applied for subgroup analysis. Time-dependent receiver-operating-characteristics (ROC) analysis was performed using R v4.1.2<sup>24</sup>. Maximally selected rank statistic optimized for the log-rank test using R v4.1.2<sup>24</sup> was performed to determine an optimal cut-off value for SUVmax.

## Results

## Patient characteristics

235 patients (Freiburg n = 39, TUM n = 56, LMU n = 64, Bologna n = 76) were included in the final analysis. 97 patients had LR only, 95 patients LN only and 43 patients LR and NR in PSMA-PET. 51% of patients received ADT, of who 59% received ADT over a duration of  $\leq 12$  months. Median follow-up was 24 months (IQR 16–41 months). No patient died during FU. See supplementary Table 2 for details.

Median SUVmax for LR and NR was 7.6 g/ml (IQR 5.3–12.8) and 7.8 g/ml (IQR 4.3–17.5), respectively. The inter-observer analysis of 15 patients revealed significantly different volumes of manually segmented PET-positive LR lesions (median 2.7ml (IQR 1.8-7.3ml) vs 1.2ml (IQR 0.5-4.1ml),  $p < 0.001$ ) but no significant differences between SUVmax values. See supplementary Fig. 1 for details.

## Cox-Regression

2-years and 4-years BRFS for all patients were 68% and 56%, respectively. For patients with LR only, 2-years and 4-years BRFS was 80% and 71%, respectively; and for patients with NR only 65% and 42%, respectively. In univariate analysis established clinical and histopathological parameters of RP were not significantly associated with BRFS. In univariate analysis, presence of LR ( $p = 0.016$ , HR 0.5 95% CI 0.3–0.9) and ADT ( $p = < 0.001$ , HR 0.4 95% CI 0.2–0.7) was associated with more favorable BRFS and the presence of NR with unfavorable BRFS ( $p = 0.007$ , HR 2.1 (95% CI 1.2–3.5)). In LR-lesions, there was a trend for association of values  $\geq$  median SUVmax (7.8 g/ml) and unfavorable BRFS ( $p = 0.071$ ), while SUVmax values  $\geq$  75% quartile (12.8 g/ml) were significantly associated with unfavorable BRFS ( $p = 0.022$ , HR 2.3 (95%CI 1.1–4.6)). In NR-lesions, no significant association of values  $\geq$  median or 75% of SUVmax (17.5 g/ml) was observed. To further assess whether SUVmax values in LR are associated with BRFS we performed a subgroup analysis with patients who only had LR (n = 97). This analysis showed again no significant association of classical clinical and histopathological parameters with BRFS, but a trend for association of values  $\geq$  median SUVmax with unfavorable BRFS ( $p = 0.05$ , HR 2.6, 95%CI 1.0–6.9), while SUVmax values  $\geq$  75% quartile were significantly associated with unfavorable BRFS ( $p = 0.001$ , HR 4.6, 95%CI 1.9–11.5). ADT was not associated with BRFS in this cohort. See Table 1 and Fig. 2 for details.

To analyze robustness a sensitivity analysis with patients with a FU of  $> 12$  months (n = 197, median FU 27 months IQR 20–43) was performed confirming the results showing no significant association of clinical and histopathological parameters with BRFS, presence of LR being significantly associated with favorable BRFS ( $p = 0.012$ , HR 0.5 95%CI 0.3–0.9) and presence of NR ( $p = 0.005$ , HR 2.2 95%CI 1.3–3.9) and SUVmax values  $\geq$  75% quartile in LR being associated with unfavorable BRFS ( $p = 0.041$ , HR 2.2 (95%CI 1.0-4.6)). Sensitivity analysis of patients with LR only and  $> 12$  months FU (n = 83) showed a strong association of SUVmax values  $\geq$  75% in LR quartile with unfavorable BRFS ( $p = 0.005$ , HR 3.9 95%CI 1.5–10.1). See Table 1 and Fig. 2.

In multivariate analysis, SUVmax values in LR  $\geq$  75% quartile stayed significantly associated with unfavorable BRFS in the cohorts including all patients ( $p = 0.022$ ) and in patients with  $> 12$  months FU ( $p = 0.041$ ). Presence of LR or NR in PET and administration of ADT was not significantly associated with BRFS in multivariate analysis. See Table 1.

## Time-dependent ROC

Time dependent ROC analysis of SUVmax values of patients with  $> 12$  months FU and  $> 12$  months FU and LR yielded a concordance-index (c-index) of 0.66 (95% CI 0.54–0.78) and 0.71 (95%CI 0.57–0.85), respectively. Prediction improved at 18 months FU. SUVmax cut-off values determined by the maximally selected rank statistic

were 11.8 g/ml for all patients and 13.0 g/ml for patients with > 12 months FU in all patients and in patients with LR only, respectively. See Fig. 3 for details and supplementary Table 3 for further analyses.

Table 1: Univariate and multivariate Cox-regression

Endpoint: BRFS

Cohort	All (n=235)				Only local recurrence (n=97)		All >12 months Follow-Up (n=197)		Only local recurrence >12 months Follow-Up (n=83)	
	n=235									
	Variable	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	
Univariate	ISUP	0.139	1.7 (0.8 – 3.5)	0.198	2.3 (0.7 – 7.7)	0.089	2.0 (0.9 – 4.4)	0.311	1.9 (0.5 – 6.7)	
	pT-stage	0.104	1.6 (0.9 – 2.7)	0.179	2.0 (0.7 – 5.6)	0.053	1.8 (1.0 – 3.3)	0.150	2.3 (0.7 – 7.0)	
	pN-stage	0.476	1.2 (0.7 – 2.1)	0.799	0.8 (0.2 – 3.6)	0.157	1.5 (0.9 – 2.7)	0.578	0.7 (0.1 – 2.9)	
	positive margin	0.153	0.7 (0.4 – 1.2)	0.814	1.1 (0.4 – 3.1)	0.359	0.8 (0.4 – 1.4)	0.738	0.8 (0.3 – 2.5)	
	Pre-sRT PSA	0.103	1.6 (0.9 – 3.0)	0.404	1.6 (0.5 – 4.8)	0.226	1.5 (0.8 – 2.6)	0.335	1.9 (0.5 – 6.5)	
	ADT	<b>&lt;0.001</b>	0.4 (0.2 – 0.7)	0.623	0.8 (0.3 – 2.0)	<b>&lt;0.001</b>	0.4 (0.2 – 0.7)	0.593	0.8 (0.3 – 2.1)	
	LR	<b>0.016</b>	0.5 (0.3 – 0.9)	-	-	<b>0.012</b>	0.5 (0.3 – 0.9)	-	-	
	NR	<b>0.007</b>	2.1 (1.2 – 3.5)	-	-	<b>0.005</b>	2.2 (1.3 – 3.9)	-	-	
	SUVmax in LR > median	0.071	2.0 (0.9 – 4.1)	0.050	2.6 (1.0 – 6.9)	0.087	2.0 (0.9 – 4.4)	0.150	2.1 (0.8 – 5.6)	
	SUVmax in LR > 75% IQR	<b>0.022</b>	2.3 (1.1 – 4.6)	<b>&lt; 0.001</b>	4.6 (1.9 – 11.5)	<b>0.049</b>	2.1 (1.0 – 4.4)	<b>0.005</b>	3.9 (1.5-10.1)	
	SUVmax in NR > median	0.640	1.1 (0.6 – 2.0)	-	-	0.786	1.1 (0.6 – 2.0)	-	-	
	SUVmax in NR > 75% IQR	0.895	1.0 (0.5 – 1.8)	-	-	0.799	0.9 (0.5 – 1.8)	-	-	
Multivariate	SUVmax LR 75% IQR	<b>0.022</b>	2.3 (1.1 – 4.6)	-	-	<b>0.049</b>	2.1 (1.0 – 4.4)	-	-	
	ADT	ns	-	-	-	ns	-	-	-	
	LR	ns	-	-	-	ns	-	-	-	
	NR	ns	-	-	-	ns	-	-	-	

*Abbreviations: BRFS: biochemical recurrence free survival, ADT= androgen deprivation therapy, ISUP= International Society of Urological Pathology Grading, pT=pathological T-stage, pN=pathological nodal stage, sRT= salvage radiotherapy, PSA=prostate specific antigen, LR= presence of local recurrence, NR=presence of nodal recurrence, SUVmax= maximal standardized uptake value, HR= hazard ratio, 95%CI=95% confidence interval), bold indicates statistical significance*

## Discussion

SRT is the last curative option for patients with recurrent or persistent PCa after surgery, but heterogeneous responses demonstrate the need for improved and differentiated risk stratification and subsequently appropriate adaptations in disease management. Whilst implementation of PSMA-PET led to relevant improvements in disease localization, with results of prospective trials pending it is not yet clear whether the sole spatial information of tumor burden and the accompanying changes in treatment management have a relevant impact on progression rates. Considering that PSMA-PET positive findings might only represent the "tip of the iceberg" the additional biological information provided by this molecular imaging bears great potential. To our knowledge, this is the first large multicenter retrospective study to evaluate the potential of SUVmax values in PSMA-PET as a new biomarker in patients with PCa persistence/recurrence. The findings from this study suggest that SUVmax values may significantly contribute to identify patients who are at higher risk for progression after sRT and therefore might benefit from treatment intensification, guiding personalized treatment approaches.

In contrary to prospective trials investigating sRT, most of the patients included in our study are likely to be at advanced recurrent disease stages with 70% having a PSA <sup>3</sup> 0.5ng/ml prior to sRT and 59% having nodal recurrence. Therefore, the comparison with data of recently published randomized controlled trials <sup>25-27</sup> is limited. Nevertheless, sRT in fossa-confined patients yielded BRFS in 71% after 4 years. Considering slightly different definitions of endpoints these results are comparable to freedom from biochemical failure in approximately 50%-70% for patients with a pre-sRT PSA between 0.2 and 2.0 ng/ml in a large retrospective study of conventionally staged patients <sup>5,28</sup>. BRFS rates for patients with node-positive PSMA-PET findings dropped dramatically to 42% after 4 years, which is in line with findings from a prospective trial, reporting 3-year BRFS rates of 45% with PSMA-PET-positive disease outside the prostatic fossa <sup>29</sup>. Our results thereby confirm, that PSMA-PET findings are highly prognostic for BRFS.

In our retrospective analysis presence of PSMA-PET positive local and nodal recurrence positive on PSMA-PET were prognosticators for BRFS after sRT, whereas classical pathological and clinical parameters were not. Since Emmet et al. prospectively demonstrated the prognostic value of PET-positive findings, it is likely that they dominate established parameters in our cohort, since we included only patients with PSMA-PET positive lesions. The improved BRFS associated with the presence of LR (HR 0.5, p=0.016) is explainable by the dose escalation of PET-positive LRs yielding sufficient RT dose coverage, which was previously reported to be beneficial <sup>10</sup>. Despite favorable outcomes, still nearly one third of patients suffered from progression after sRT. In multivariate analysis our results demonstrate a significant association of SUVmax <sup>3</sup> 75% quartile (HR 2.3, p=0.022) with unfavorable BRFS in this subgroup.

Sensitivity analysis confirmed these results with a HR of 3.9 in patients with LR only and FU of >12 months. These findings are in line with the biological understanding of PSMA, with high PSMA-expression being associated with more aggressive disease <sup>30</sup> and SUVmax correlating with PSMA-expression <sup>31</sup>. Therefore, patients with LR and

high SUVmax values might represent a subgroup with more aggressive PCa, potentially suffering from micro metastases outside the prostatic bed at the time of imaging and therefore benefiting from intensified treatments. Cox-regression and ROC analysis furthermore suggest, that SUVmax in LR might be a valuable prognosticator in patients with both, LRs and NR. However, these results need to be interpreted carefully, since ADT is administered more often and for a longer period of time in patients with NR (44% in our cohort).

Whether extraction of additional radiomic features from PSMA-PET images enables identification of additional prognosticators<sup>32</sup> needs to be evaluated in future studies. However, implementation of SUVmax offers great potential in this scenario, since it is easily and non-invasively determinable with minimal resources and without additional costs and is not affected by interobserver variability<sup>33</sup>. AUC values of the time-dependent ROC analysis showed the best discrimination in patients with >12 months FU and LR only. In an exploratory analysis, we calculated SUVmax cut-off value for optimal discrimination. In all patients, the optimized cut-off value was slightly lower than the 75% quartile (11.8 g/ml vs 12.8 g/ml). In the subgroup with FU > 12 months the cut-off value was, however, more similar (13 g/ml). Thus, a SUVmax threshold of approximately 13.0 g/ml should be validated in future studies in PSMA-PET imaging. This being said, the role of SUVmax in these patient subgroups needs to be evaluated in future studies including new tracers to validate putative cut-off values and design studies, which evaluate treatment intensification such as extension of RT fields to elective nodes or intensified systemic treatments. To define optimal RT fields, patterns of metastases need to be vigorously analyzed. Intensification of systemic treatments in sRT is currently investigated by the FORMULA-059 RCT (NCT03141671). Keeping in mind that sRT should be initiated at low PSA levels, implementation of SUVmax into risk stratification might even be relevant in this scenario, with approximately 50% and 65% of patients having PET-positive findings at PSA values <0.2ng/ml and between 0.2 - 0.5 ng/ml<sup>29</sup>. Furthermore, administration of ADT was associated with favorable BRFS in the entire cohort in univariate analysis, but not in multivariate analysis. Additionally ADT was not associated with BRFS in patients with LR only. This suggests, that these patients might rather benefit from local than from systemic treatment intensification.

Interestingly presence of NR was associated with significantly unfavorable BRFS (HR 2.1) but not SUVmax values in NR, suggesting that the additional biologic information provided by SUVmax values do not contribute to this patient subgroup, who already suffer from relevantly poorer prognosis. These patients might benefit from systemic treatment intensification, since despite dose escalation to PET positive nodes, it is likely that sRT might not cover non-visible tumor spread.

Our study has some limitations. First, due to its retrospective design, protocols for PSMA-PET scans, sRT and follow-up varied between centers and are prone to selection bias. Since the tracer kinetics depends on the time between injection and image acquisition we want to point out that all scans were acquired in line with recent guidelines in all centers, but use of different PET scanners might affect comparability. Second, no central review of PET images was performed with potential differences in interpretation between centers. Third, the median FU is relatively short with a median FU of 24 months. Lastly pathological data from RP was missing in up to 27% of patients, likely contributing to inferior Cox-regression results.

## Conclusion

Our study is the first to demonstrate that the SUVmax value is a promising new non-invasive biomarker to prognosticate outcome in patients undergoing sRT and recurrence confined to the prostatic fossa ± nodal

recurrences in PSMA-PET. Its addition might contribute to improve risk stratification of patients with recurrent PCa and to guide personalized treatment decisions.

## Declarations

### Disclosure

ME reports prior consulting activities for BED, Novartis, Telix, Progenics, Bayer, Point Biopharma and Janssen and a patent application for rhPSMA. All other authors declare no conflicts of interest regarding this study.

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### Author contribution:

SKBS, AF, CZ and JCP contributed to the study conception and design. Material preparation and data collection was performed by SKBS, AF, SS, MV, HL, FS, JAB, CT, NS and JCP. SKBS, AF, JR, MM, SK, FC, SF, CG, AS, SEC, DB, JEG, CB, PB, ME, SGN, KS, ALG, NS, CZ, JCP were responsible for evaluation of patient treatment, image findings and their interpretation. FC, SF, CG, CB, SEC and ALG supervised this study. SKBS, AF, JCP and CZ performed data analysis. The first draft of the manuscript was written by SKBS, AF, CZ and JCP. All authors were involved in review of the manuscript and approved the final manuscript.

### Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## References

1. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the Outcome of Salvage Radiation Therapy for Recurrent Prostate Cancer After Radical Prostatectomy. *Journal of Clinical Oncology*. 2007;25(15):2035-2041. doi:10.1200/jco.2006.08.9607
2. Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *Jama*. Mar 17 2004;291(11):1325-32. doi:10.1001/jama.291.11.1325
3. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant Radiotherapy Versus Wait-and-See After Radical Prostatectomy: 10-year Follow-up of the ARO 96–02/AUO AP 09/95 Trial. *European Urology*. 2014/08/01/2014;66(2):243-250. doi:https://doi.org/10.1016/j.eururo.2014.03.011
4. Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. *Eur Urol*. Feb 2021;79(2):263-282. doi:10.1016/j.eururo.2020.09.046
5. Tendulkar RD, Agrawal S, Gao T, et al. Contemporary Update of a Multi-Institutional Predictive Nomogram for Salvage Radiotherapy After Radical Prostatectomy. *Journal of Clinical Oncology*. 2016;34(30):3648-3654. doi:10.1200/jco.2016.67.9647
6. Banerjee SR, Pullambhatla M, Byun Y, et al. <sup>68</sup>Ga-labeled inhibitors of prostate-specific membrane antigen (PSMA) for imaging prostate cancer. *J Med Chem*. Jul 22 2010;53(14):5333-41. doi:10.1021/jm100623e

7. Fendler WP, Calais J, Eiber M, et al. Assessment of 68Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial. *JAMA Oncol.* Jun 1 2019;5(6):856-863. doi:10.1001/jamaoncol.2019.0096
8. Farolfi A, Ceci F, Castellucci P, et al. (68)Ga-PSMA-11 PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy and PSA <0.5 ng/ml. Efficacy and impact on treatment strategy. *Eur J Nucl Med Mol Imaging.* Jan 2019;46(1):11-19. doi:10.1007/s00259-018-4066-4
9. Schmidt-Hegemann N-S, Eze C, Li M, et al. Impact of <sup>68</sup>Ga-PSMA PET/CT on the Radiotherapeutic Approach to Prostate Cancer in Comparison to CT: A Retrospective Analysis. *Journal of Nuclear Medicine.* 2019;60(7):963-970. doi:10.2967/jnumed.118.220855
10. Schmidt-Hegemann N-S, Zamboglou C, Thamm R, et al. A Multi-Institutional Analysis of Prostate Cancer Patients With or Without 68Ga-PSMA PET/CT Prior to Salvage Radiotherapy of the Prostatic Fossa. Original Research. *Frontiers in Oncology.* 2021-October-01 2021;11(3991)doi:10.3389/fonc.2021.723536
11. Han S, Woo S, Kim YJ, Suh CH. Impact of (68)Ga-PSMA PET on the Management of Patients with Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol.* Aug 2018;74(2):179-190. doi:10.1016/j.eururo.2018.03.030
12. Schmidt Hegemann NS, Rogowski P, Eze C, et al. Outcome After 68Ga-PSMA-11 versus Choline PET-Based Salvage Radiotherapy in Patients with Biochemical Recurrence of Prostate Cancer: A Matched-Pair Analysis. *Cancers (Basel).* Nov 16 2020;12(11)doi:10.3390/cancers12113395
13. Schmidt-Hegemann N-S, Stief C, Kim T-H, et al. Outcome after PSMA PET/CT based salvage radiotherapy in patients with biochemical recurrence after radical prostatectomy: a bi-institutional retrospective analysis. *Journal of Nuclear Medicine.* 2018;jnumed.118.212563. doi:10.2967/jnumed.118.212563
14. Calais J, Czernin J, Fendler WP, Elashoff D, Nickols NG. Randomized prospective phase III trial of (68)Ga-PSMA-11 PET/CT molecular imaging for prostate cancer salvage radiotherapy planning [PSMA-SRT]. *BMC Cancer.* Jan 7 2019;19(1):18. doi:10.1186/s12885-018-5200-1
15. Jiao J, Kang F, Zhang J, et al. Establishment and prospective validation of an SUV(max) cutoff value to discriminate clinically significant prostate cancer from benign prostate diseases in patients with suspected prostate cancer by (68)Ga-PSMA PET/CT: a real-world study. *Theranostics.* 2021;11(17):8396-8411. doi:10.7150/thno.58140
16. Roberts MJ, Morton A, Donato P, et al. (68)Ga-PSMA PET/CT tumour intensity pre-operatively predicts adverse pathological outcomes and progression-free survival in localised prostate cancer. *Eur J Nucl Med Mol Imaging.* Feb 2021;48(2):477-482. doi:10.1007/s00259-020-04944-2
17. Uprimny C, Kroiss AS, Decristoforo C, et al. (68)Ga-PSMA-11 PET/CT in primary staging of prostate cancer: PSA and Gleason score predict the intensity of tracer accumulation in the primary tumour. *Eur J Nucl Med Mol Imaging.* Jun 2017;44(6):941-949. doi:10.1007/s00259-017-3631-6
18. Wang Z, Zheng A, Li Y, et al. 18F-PSMA-1007 PET/CT Performance on Risk Stratification Discrimination and Distant Metastases Prediction in Newly Diagnosed Prostate Cancer. Original Research. *Frontiers in Oncology.* 2021-October-28 2021;11(4505)doi:10.3389/fonc.2021.759053
19. Fendler WP, Eiber M, Beheshti M, et al. (68)Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. *Eur J Nucl Med Mol Imaging.* Jun 2017;44(6):1014-1024. doi:10.1007/s00259-017-3670-z

20. Ceci F, Oprea-Lager DE, Emmett L, et al. E-PSMA: the EANM standardized reporting guidelines v1.0 for PSMA-PET. *European Journal of Nuclear Medicine and Molecular Imaging*. 2021/05/01 2021;48(5):1626-1638. doi:10.1007/s00259-021-05245-y
21. Eiber M, Herrmann K, Calais J, et al. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): Proposed miTNM Classification for the Interpretation of PSMA-Ligand PET/CT. *J Nucl Med*. Mar 2018;59(3):469-478. doi:10.2967/jnumed.117.198119
22. Fedorov A, Beichel R, Kalpathy-Cramer J, et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magn Reson Imaging*. 2012;30(9):1323-1341. doi:10.1016/j.mri.2012.05.001
23. Zamboglou C, Fassbender TF, Steffan L, et al. Validation of different PSMA-PET/CT-based contouring techniques for intraprostatic tumor definition using histopathology as standard of reference. *Radiother Oncol*. Dec 2019;141:208-213. doi:10.1016/j.radonc.2019.07.002
24. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2021;
25. Kneebone A, Fraser-Browne C, Duchesne GM, et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. *Lancet Oncol*. Oct 2020;21(10):1331-1340. doi:10.1016/s1470-2045(20)30456-3
26. Parker CC, Clarke NW, Cook AD, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. *Lancet*. Oct 31 2020;396(10260):1413-1421. doi:10.1016/s0140-6736(20)31553-1
27. Sargos P, Chabaud S, Latorzeff I, et al. Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. *Lancet Oncol*. Oct 2020;21(10):1341-1352. doi:10.1016/s1470-2045(20)30454-x
28. Pisansky TM, Agrawal S, Hamstra DA, et al. Salvage Radiation Therapy Dose Response for Biochemical Failure of Prostate Cancer After Prostatectomy-A Multi-Institutional Observational Study. *Int J Radiat Oncol Biol Phys*. Dec 1 2016;96(5):1046-1053. doi:10.1016/j.ijrobp.2016.08.043
29. Emmett L, Tang R, Nandurkar R, et al. 3-Year Freedom from Progression After <sup>68</sup>Ga-PSMA PET/CT–Triaged Management in Men with Biochemical Recurrence After Radical Prostatectomy: Results of a Prospective Multicenter Trial. *Journal of Nuclear Medicine*. 2020;61(6):866-872. doi:10.2967/jnumed.119.235028
30. Hupe MC, Philippi C, Roth D, et al. Expression of Prostate-Specific Membrane Antigen (PSMA) on Biopsies Is an Independent Risk Stratifier of Prostate Cancer Patients at Time of Initial Diagnosis. Original Research. *Frontiers in Oncology*. 2018-December-20 2018;8(623)doi:10.3389/fonc.2018.00623
31. Woythal N, Arsenic R, Kempkensteffen C, et al. Immunohistochemical Validation of PSMA Expression Measured by (68)Ga-PSMA PET/CT in Primary Prostate Cancer. *J Nucl Med*. Feb 2018;59(2):238-243. doi:10.2967/jnumed.117.195172
32. Spohn SKB, Bettermann AS, Bamberg F, et al. Radiomics in prostate cancer imaging for a personalized treatment approach - current aspects of methodology and a systematic review on validated studies. *Theranostics*. 2021;11(16):8027-8042. doi:10.7150/thno.61207
33. Miksch J, Bottke D, Krohn T, et al. Interobserver variability, detection rate, and lesion patterns of 68Ga-PSMA-11-PET/CT in early-stage biochemical recurrence of prostate cancer after radical prostatectomy. *European*

## Figures

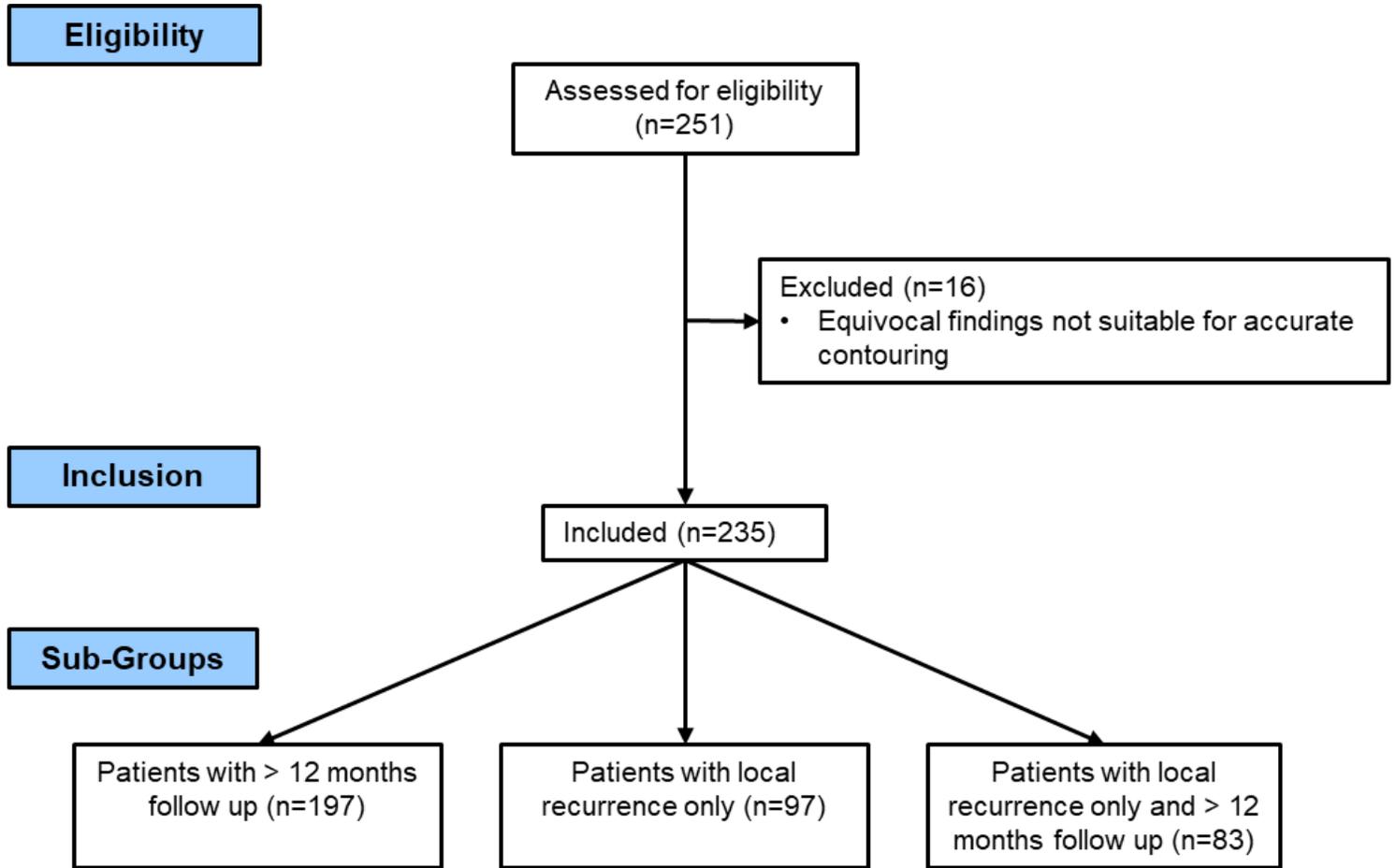
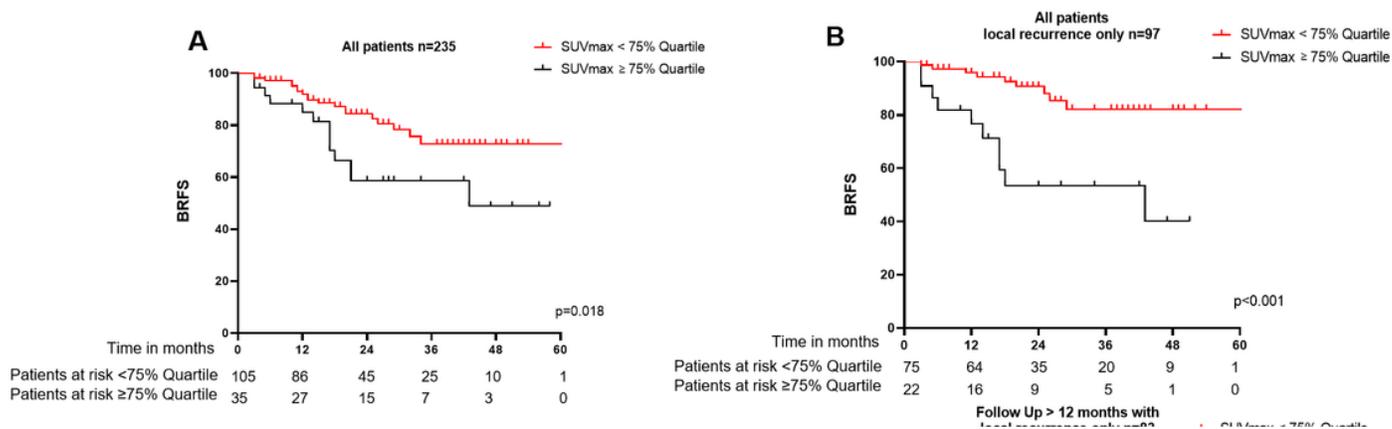


Figure 1

Consort flow diagram

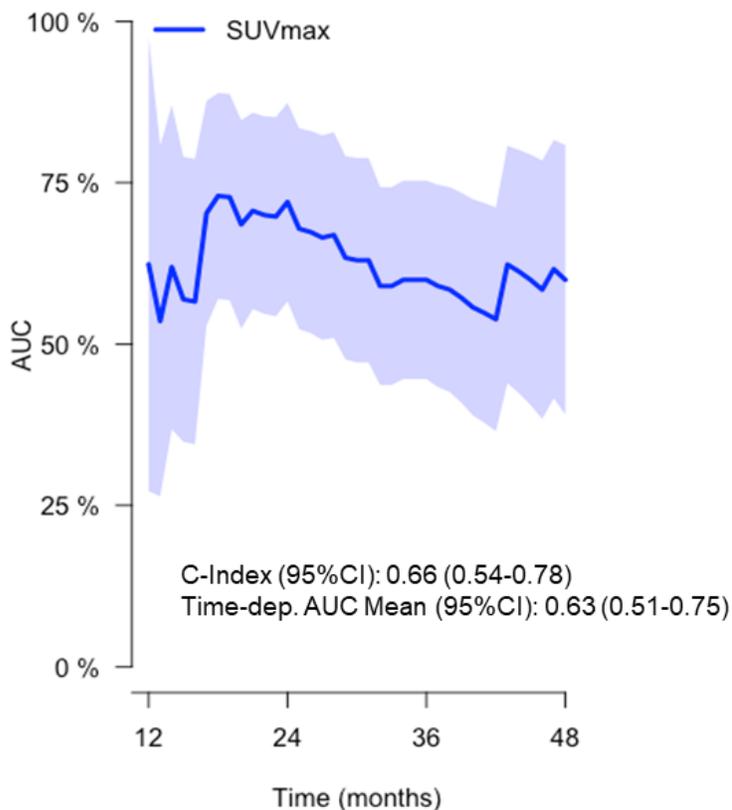


**Figure 2**

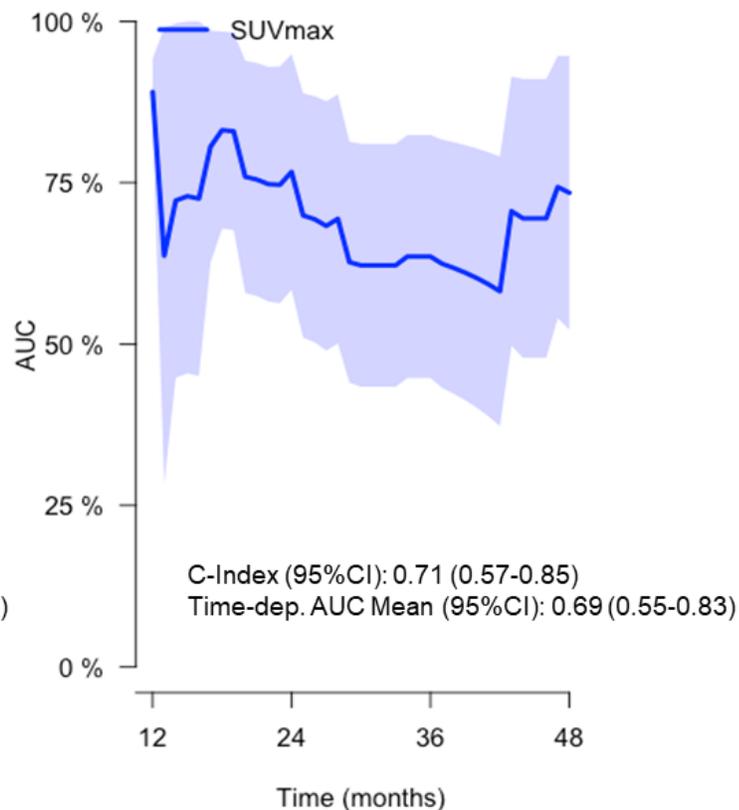
Kaplan-Meier curves for BRFs according to SUVmax values in different subgroups.

Kaplan-Meier curves are represented for the impact of maximal standardized uptake values (SUVmax) <sup>3</sup> 75% quartile or < 75% quartile in local recurrences on biochemical recurrence free survival (BRFS). Statistical comparison was performed with log-rank test.

### Follow Up > 12



### Follow Up > 12 months and local recurrence only



**Figure 3**

Time-dependent receiver-operator-characteristics (ROC) analysis of the maximal standardized uptake value (SUVmax). Concordance Index (C-Index) and area-under-the-curve values (AUC) with 95% confidence interval (95%CI) are shown. Transparent area demonstrates the 95%CI.

## Supplementary Files

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