



# Decision-support for treatment with $^{177}\text{Lu}$ -PSMA: machine learning predicts response with high accuracy based on PSMA-PET/CT and clinical parameters

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**Background:** Treatment with radiolabeled ligands to prostate-specific membrane antigen (PSMA) is gaining importance in the treatment of patients with advanced prostate carcinoma. Previous imaging with positron emission tomography/computed tomography (PET/CT) is mandatory. The aim of this study was to investigate the role of radiomics features in PSMA-PET/CT scans and clinical parameters to predict response to  $^{177}\text{Lu}$ -PSMA treatment given just baseline PSMA scans using state-of-the-art machine learning (ML) methods.

**Methods:** A total of 2,070 pathological hotspots annotated in 83 prostate cancer patients undergoing PSMA therapy were analyzed. Two main tasks are performed: (I) analyzing correlation of averaged (per patient) values of radiomics features of individual hotspots and clinical parameters with difference in prostate specific antigen levels ( $\Delta\text{PSA}$ ) in pre- and post-therapy as a therapy response indicator. (II) ML-based classification of patients into responders and non-responders based on averaged features values and clinical parameters. To achieve this, machine learning (ML) algorithms and linear regression tests are applied. Grid search, cross validation (CV) and permutation test were performed to assure that the results were significant.

**Results:** Radiomics features (PET\_Min, PET\_Correlation, CT\_Min, CT\_Busyness and CT\_Coarseness) and clinical parameters such as Alp1 and Gleason score showed best correlations with  $\Delta\text{PSA}$ . For the treatment response prediction task, 80% area under the curve (AUC), 75% sensitivity (SE), and 75% specificity (SP) were obtained, applying ML support vector machine (SVM) classifier with radial basis function (RBF) kernel on a selection of radiomics features and clinical parameters with strong correlations with  $\Delta\text{PSA}$ .

**Conclusions:** Machine learning based on  $^{68}\text{Ga}$ -PSMA PET/CT radiomics features holds promise for the prediction of response to  $^{177}\text{Lu}$ -PSMA treatment, given only base-line  $^{68}\text{Ga}$ -PSMA scan. In addition, it was shown that, the best correlating set of radiomics features with  $\Delta\text{PSA}$  are superior to clinical parameters for this therapy response prediction task using ML classifiers.

**Keywords:** Prostate cancer (PC); prostate specific membrane antigen (PSMA); positron emission tomography

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(PET); computed tomography (CT); machine learning (ML)

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## Introduction

Machine learning (ML) has gained essential importance in therapy planning and patient selection for certain treatments recently (1,2). The role of radiomics features for patients screening for certain therapies has been under investigation as well (3,4). Prostate cancer (PC) is one of the most common malignancies in men worldwide. If spread beyond the prostate it can lead to a significant mortality (5). Although treatment of advanced PC has improved significantly in recent years, more than 250,000 fatalities are caused by PC per year.

Radioligand therapy targeting the prostate specific membrane antigen (PSMA) gained great importance in the last years and a clear benefit for patients who do not respond to any other available treatment was shown (6). In these patients, pretherapeutic imaging is performed using PSMA analogues labeled mainly with positron emitters Gallium-68 or Fluorine-18 as theranostics approach (7). However, about 10% to 32% of the patients show progressive disease during treatment with <sup>177</sup>Lu-PSMA (8). Therefore strategies to differentiate patients who may benefit from therapy from patients who may not benefit are of great importance. Pretherapeutic PSMA positron emission tomography/computed tomography (PET/CT) scans as well as different clinical parameters like initial Gleason score or serum levels of prostate-specific antigen (PSA) have been investigated for this purpose without clear findings (9).

In the past years, radiomics features such as textural parameters have been gaining importance in the analysis of PET/CT data. The significance of textural features analysis in diagnosis and therapy response prediction using PSMA PET/CT scan has been shown as well (3,4,10,11). Our previous findings showed that machine learning (ML) can facilitate detection of pathological uptake in <sup>68</sup>Ga-PSMA PET/CT scans with nuclear medicine (NM) expert accuracy (12). Also, for the prediction of treatment response to <sup>177</sup>Lu-PSMA therapy in PC patients first results have been published by Khurshid *et al.* showing that there is a significant correlation between the mean homogeneity and entropy of PET scans as patient-based textural features on the one hand, and the PSA level difference as a therapy

response indicator on the other hand (13). While many studies aimed at analyzing the correlation between each clinical or textural parameter and tumor malignancy or therapy response, respectively (11,13), many ML methods are available that outperform independent feature analyses by combining several parameters to perform similar tasks (1,2,12).

In the presented study, we propose a method for treatment response prediction in patients undergoing <sup>177</sup>Lu-PSMA therapy. In the first step, the baseline scans are manually annotated to detect the pathological uptakes of the whole cohort resulting in 2070 hotspots. Then, the radiomics features of all the annotated hotspots are calculated individually. Afterwards, linear regression is performed to identify best correlating features and clinical parameters with changes in PSA-level as surrogate marker for treatment response and survival (14). Finally, ML methods are applied on different combinations of the features and clinical parameters to predict response to <sup>177</sup>Lu-PSMA treatment. We aim at quantifying the classification accuracy of different ML classifiers for the prediction task.

We present the following article in accordance with the MDAR checklist (available at <http://dx.doi.org/10.21037/atm-20-6446>).

## Methods

### *Patients and Volume of interest (VoI) definition and annotation*

A total of 83 male patients with advanced PC scheduled for treatment with <sup>177</sup>Lu-PSMA were included in this retrospective analysis. The patients' age range varied from 48 to 87 years and their Gleason score ranged from 6 to 10. The serum PSA level range of the cohort was between 4.7 and 5,910 ng/mL. All patients underwent pretherapeutic <sup>68</sup>Ga-PSMA PET/CT scans 5 to 21 days before the beginning of the treatment. The scans were carried out between November 2014 and August 2019. About 40 to 80 minutes after intravenous injection of 98 to 159 MBq in-house produced <sup>68</sup>Ga-HBED-CC PSMA, a Biograph 2 PET/CT system (Siemens Medical Solutions, Erlangen,

**Table 1** List of the radiomics features from both PET and CT modalities. Please note that the total lesion glycolysis (TLG is PET-specific)

First or higher order statistics	Shape and size	Textural	Volumetric zone length statistics	Volumetric run length statistics
Deviation	Max. diameter	Entropy	Short zone emphasis	Short run emphasis
Mean		Homogeneity	Long zone emphasis	Long run emphasis
Max		Correlation	Low grey-level zone emphasis	Low grey-level run emphasis
Min		Contrast	High grey-level zone emphasis	High grey-level run emphasis
Sum		Size variation	Short zone low grey-level emphasis	Short run low grey-level emphasis
PET-TLG		Intensity variation	Short zone high grey-level emphasis	Short run high grey-level emphasis
Kurtosis		Coarseness	Long zone low grey-level emphasis	Long run low grey-level emphasis
		Busyness	Long zone high grey-level emphasis	Long run high grey-level emphasis
		Complexity	Zone percentage	Grey-level non-uniformity
				Run length non-uniformity
				Run percentage

PET, positron emission tomography; CT, computed tomography.

Germany) was used to take the low-dose CT (16 mAs, 130 kV) from the base of skull to mid thigh. Then, the PET scan acquired over the same area with 3 or 4 minutes per bed position depending on the body weight of the patient. The PET data were reconstructed in 128 by 128 matrices with 5 mm slices thickness. The CT data were reconstructed in 512 to 512 matrices with 5 mm slice thickness. As implemented by the manufacturer, an attenuation-weighted ordered subsets expectation maximization algorithm was utilized for attenuation and scatter corrections (8 iterations, 16 subsets), a 5 mm Gaussian post-reconstruction-filter was applied afterwards. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients gave written and informed consent to the imaging procedure and for anonymized evaluation and publication of their data. Due to the retrospective character of the data analysis an ethical statement was waived by the institutional ethical review board according to the professional regulations of the medical board of Nordrheinwestfalen, Germany.

For each scan, all the pathological hotspots have been identified and delineated by a trained nuclear medicine physician (NM) (board certified with 7 years' experience in PET/CT analysis) using InterView Fusion software (Mediso Medical Imaging, Hungary, Version 3.08.005). The hotspots include the primary tumor if present as well as metastatic uptakes in any organs. Per hotspot, a total of 73 (37 PET-based + 36 CT-based) features were calculated

(Table 1). The features include first and higher order statistics features (mean, max, kurtosis, etc.), shape based features (max diameter and volume), textural features (entropy, contrast, homogeneity, etc.), and volumetric zone and run length statistics (grey-level non-uniformity, short run emphasis, etc.).

In addition to the radiomics features, fourteen numerical clinical parameters have been taken into account for each individual patient. These clinical parameters include age, weight, height as well as therapeutic parameters such as Gleason score, ALP1 and base-line serum PSA level. For the detailed list of the clinical parameters, see Table 2.

According to previous findings (14) and as surrogate markers for treatment response, prostate specific antigen (PSA) serum values have been collected at the time point of the PET/CT examination and seven to eight weeks after the treatment. Changes in PSA levels ( $\Delta$ PSA) between these time-points have been used for further analyses. Based on the calculated  $\Delta$ PSA values, out of the 83 patients, 59 and 24 patients have been classified as responders and non-responders respectively.

### Statistical analysis

#### Linear regression

After accumulating the data from all the scans, radiomics features and clinical parameters of individual patients were combined to form feature vectors for further analyses.

**Table 2** Descriptions of the numerical clinical parameters

Parameter	Description
Age	Age at the first PSMA PET
Weight	Weight at the first PSMA PET
Height	Height at the first PSMA PET
Gleason score	Describes abnormality degree of cancer cells in prostate
ALP1	Serum alkaline phosphatase at the first PSMA PET
PSA1	Serum PSA level at the first PSMA PET
Time difference	Time between the first diagnosis and the first PSMA PET
Crea1	Serum creatinine at the first PSMA PET
CRP1	C-reactive protein in serum at the first PSMA PET
Hb1	Hemoglobin at the first PSMA PET
Ery1	Erythrocytes at the first PSMA PET
Thrombose1	Thrombocytes at the first PSMA PET
Leukos1	Leicozytes at the first PSMA PET

PSMA, prostate specific membrane antigen; PET, positron emission tomography.

To achieve these, the values of the radiomics features of the individual pathological hotspots of each patient were averaged to calculate the mean values of the features. The clinical parameters of the individual patients were then merged with their corresponding radiomics features.

To correlate individual features and clinical parameters with  $\Delta$ PSA, linear regression has been used for all the 73 features and 14 numerical clinical parameters. The  $\Delta$ PSA is calculated by subtracting the PSA level at the post therapy scan from the corresponding PSA level at the pre-therapy scan. Therefore, a negative value of  $\Delta$ PSA means the patient had responded to the  $^{177}\text{Lu}$ -PSMA therapy and vice versa.

As the numbers of responders and non-responders (59 and 24 patients respectively) to the  $^{177}\text{Lu}$ -PSMA therapy in the original cohort did not match, for the linear regression task, a balanced subset of the cohort with 24 patients in each category of responders or non-responder was formed. The 24 responders have been randomly selected out of the whole 59 responders (the demographic and physiological distributions were maintained during the sub-sampling). As will be described in the classification and cross-validation (CV) sub-sections, each of the balanced

and unbalanced cohorts were sub-divided into training and validation data-sets to assess the prediction performance for the classification task. Hence, the linear regression analyses have been conducted on training data-sets of balanced and unbalanced cohorts separately. As a result, best sets of radiomics features and clinical parameters which had strong correlations (P value  $<0.05$ ) with  $\Delta$ PSA were identified for both balanced and unbalanced groups. These best correlating features and parameters were used for the analyses of treatment response prediction in the further steps. This strategy of identifying the best correlating parameters by only considering training cohorts helps to avoid over-fitting (15).

### Classification

As support vector machines (SVMs) and decision tree based methods are widely used for clinical treatment outcome prediction [e.g., prediction outcome of chemotherapy (16), prediction of optimal cancer drug therapies (17), and risk stratification in primary prostate cancer (18)], we have applied several classifiers from these groups for the therapy response prediction task. The five ML classifiers [linear, radial basis function (RBF), and polynomial kernel SVM (19), ExtraTrees (20), and RandomForest (21)] were used to investigate the relative importance of different groups of radiomics features and clinical parameters. The accuracy measures [area under the curve (AUC), sensitivity (SE), and specificity (SP)] are averaged to calculate the total precision for each of the tasks. Thus, for each pair of classifier and feature group, we calculate AUC, SE, and SP separately.

### Cross-validation (CV)

It is essential to have separate data for hyperparameter tuning and for quantifying final accuracy to achieve generalizable results and to avoid over-fitting. To this end, two different CV steps are taken. In the first step, the whole data-set with 83 patients, including 59 responders and 24 non-responders, is taken into account. In the second step, a balanced subset of the cohort with 48 subjects (the same subset as used for the prior linear regression task) is used for CV. This strategy of having an extra CV step based on a balanced cohort helps to identify if the classifiers' scores on the unbalanced cohort were realistic.

### Unbalanced cohort

First, the whole cohort of 83 patients was randomly sub-divided into two subsets: (I) the training cohort with 56 subjects, and (II) the validation or hold-out set with 27

subjects. The demographics and clinical states of the cohorts were similar. The ratios of responders to non-responders in the training and validation sets were also comparable. To standardize and normalize the data, MinMaxScaler method (22) was used. Stratified-KFold CV with 3 folds applied to the training cohort for hyperparameter tuning.

In each CV step, a grid search has been performed to find the best set of parameters for each of the ML algorithms to predict the true labels for each category. For the grid search, several parameters with wide ranges of values ( $C=[1, 10, 100, 1000, 2^{-5}, 2^{-3}, \dots, 2^{15}]$ ,  $\text{gamma}=[1e-3, 1e-4, 2^{-15}, 2^{-13}, 2^{-11}, \dots, 2^3]$ , etc.) were used to fine-tune the ML classifiers.

After tuning the best set of hyperparameters for each ML method based on the accuracies achieved on the training cohort, the prediction performances of the ML classifiers were quantified, comparing with the ground truth labels from the hold-out cohort. Again, the relative importance of different radiomics features groups and clinical parameters were analyzed individually.

#### **Balanced cohort**

As the numbers of the responder and non-responder groups did not match, additional CV steps have been taken based on a balanced subset of the cohort with 48 patients (including 24 responders and 24 non-responders). This balanced cohort was separated into training and validation sets as well. This time, the training cohort consisted of 32 subjects and the validation or hold-out set consisted of 16 patients. Again, the responder to non-responder ratio was equal in both of the training and validation subsets. Similar to the first CV step (for the unbalanced cohort), stratified KFold with 3 folds have been applied on the training set to fine-tune the hyperparameters, including standardization of the feature values as well as grid search on each CV iteration. Afterwards, as the final validation step and for each classifier applied to each group of features or clinical parameters, prediction accuracies were calculated on the validation subset. Finally, the accuracy measures of each classifier on each feature group applied to the validation (hold-out) cohort will be reported as the achieved performance.

#### **Permutation test**

To assure that the results are significant, a permutation test is performed. The permutation test rejected the null hypothesis which stated that permuted distribution of ground truth labels could have resulted in similar prediction scores. Hence, a separate three-fold CV on the cohort with

32 patients from the second CV step is conducted. There were 80,000 total iterations with exactly similar groups of radiomics features and clinical parameters as well as ML classifiers as for the prior CV steps. In each CV step, the ground truth binary labels were permuted. All the AUCs equal to or higher than the threshold of 0.61 (the worst AUC achieved by our classifiers on the hold-out set) are counted. Then, to calculate the P value of the permutation test, the resulting number is divided by the total number of iterations [80,000]:

$$p = \frac{n(AUCs \geq thr)}{N} \quad [1]$$

where  $p$  is the P value of the permutation test,  $n()$  is the number of the test scores over the given threshold ( $thr$ ),  $AUCs$  are the calculated areas under the ROC curves for each classifier on each feature group at each iteration, and  $N$  is the total number of iterations (Eq. [1]).

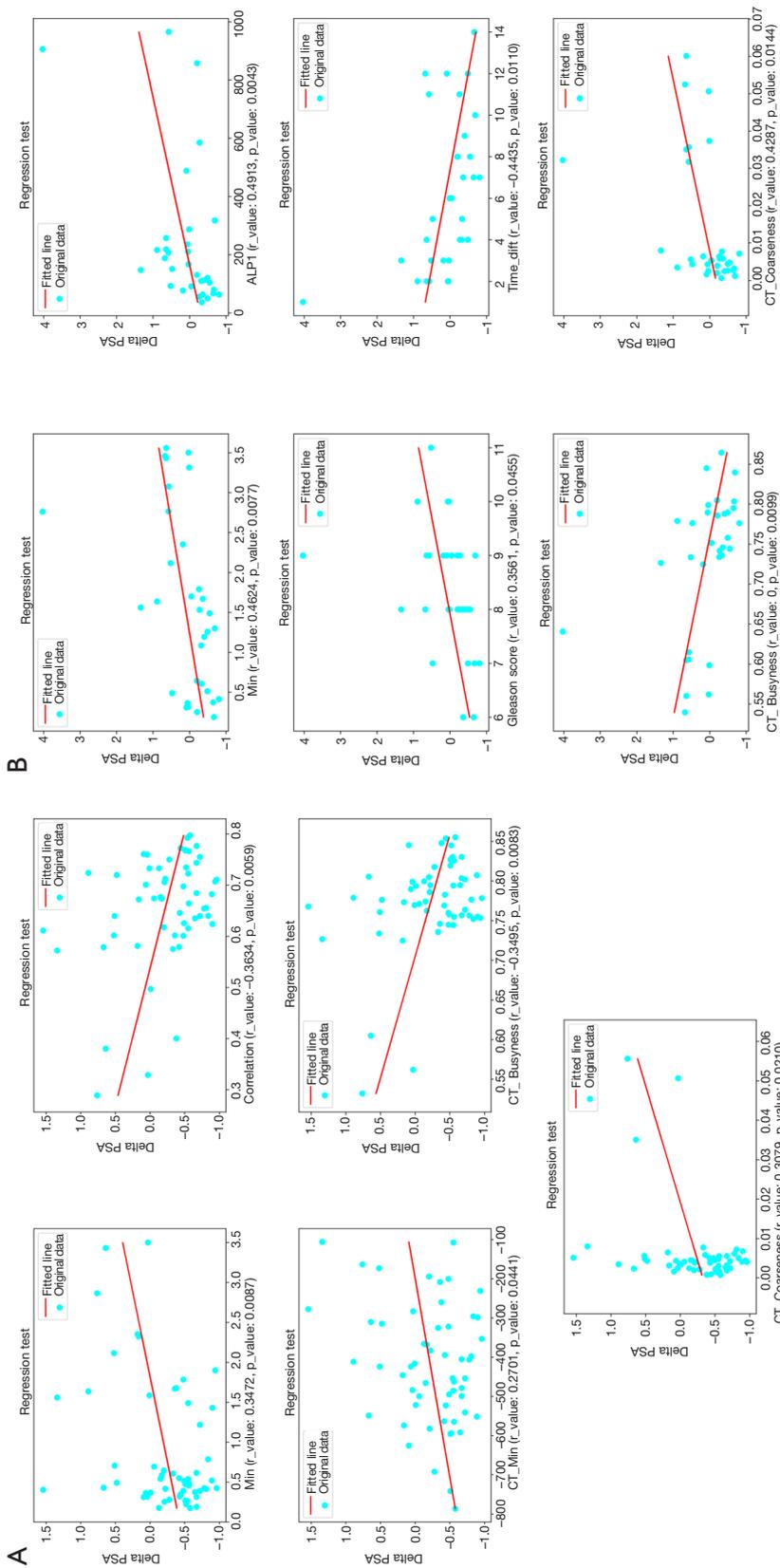
## **Results**

### **Linear regression-unbalanced cohort**

Among all the 73 radiomics features and 14 numerical clinical parameters, the linear regression tests on the training set of the unbalanced cohort illustrated that 5 radiomics features from both PET (Min and Correlation) and CT (CT\_Min, CT\_Coarseness, and CT\_Busyness) modalities (named best correlating features or Best-Radiomics from now on) have the best correlation scores with PSA level difference (P values  $<0.05$ ) as the surrogate marker for therapy response. *Figure 1A* shows the regression diagrams of the 5 best correlating features with  $\Delta$ PSA. *Table 3* shows these 5 features and their corresponding r- and P values of the regression tests on the unbalanced group.

### **Linear regression-balanced cohort**

As for the unbalanced cohort, the linear regression analyses on the training set of the balanced cohort resulted in a group of 3 radiomics features (PET\_Min, CT\_Busyness, and CT\_Coarseness) and 3 clinical parameters (Alp1, Time difference, and Gleason score). The results are shown in *Figure 1B* and *Table 4*. For further analyses, two different groups of best correlating parameters are created. First group (Best-Radiomics) includes only the best correlating radiomics features and the second group (Best-



**Figure 1** Linear regression diagrams: (A) for the best correlating features with PSA level difference from the unbalanced cohort with 56 subjects; (B) for the best correlating radionomics features and clinical parameters with PSA level difference from the training data-set of the balanced cohort with 32 subjects. PSA, prostate specific antigen.

**Table 3** List of the 5 best correlating radiomics features with PSA level change with their corresponding r- and P values on the training data-set of the unbalanced cohort with 56 subjects

Feature/parameter	r-value	P value
Min	0.3472	0.0087
Correlation	-0.3634	0.0059
CT_Min	0.2701	0.0441
CT_Coarseness	0.3079	0.0210
CT_Busyness	-0.3495	0.0083

PSA, prostate specific antigen; CT, computed tomography.

**Table 4** List of the best correlating radiomics features [3] and clinical parameters [3] with PSA level change with their corresponding r- and P values on the training data-set of the balanced cohort with 32 subjects

Feature/parameter	r-value	P value
Alp1	0.4913	0.0043
Gleason score	0.3561	0.0455
Time difference	-0.4435	0.0110
Min	0.4624	0.0077
CT_Coarseness	0.4287	0.0144
CT_Busyness	-0.4492	0.0099

PSA, prostate specific antigen; CT, computed tomography.

Mixed) includes features or parameters which had strong correlation with  $\Delta$ PSA from both of the radiomics and clinical groups.

### **Classification-unbalanced cohort**

As shown in *Table 5*, the SVM classifier with RBF kernel had the best performance (83% AUC, 99% SE, and 99% SP) on the best correlating radiomics features with  $\Delta$ PSA (named Best-Radiomics group) in the first CV step on the unbalanced training cohort with 56 subjects. The relatively low values of specificity for some classifiers applied to all the radiomics features or the mixture of all the 73 radiomics features and 14 numerical clinical parameters (named the Mixed group) reflect the unbalanced characteristic of the cohort.

Based on the grid search results on the CV step, hyperparameters of each classifier have been tuned (*Table 6*). These tuned values for the parameters have

been used in the validation step to calculate the prediction score of the classifiers as applied to the hold-out set. In the validation step, the cohort of 56 subjects was used as the training data-set and the cohort of 27 subjects was used as the test set. The results of this validation step is shown in *Table 7* and *Figure 2*. Here, the clinical parameters group showed relatively weak scores, compared to the scores achieved by the other groups. The results reveal that the polynomial kernel SVM with parameters degree =3 and C=1 had the best performance as applied to the mixture of all radiomics and clinical values (99% AUC, 84% SE, and 99% SP). Also, the SVM classifier with linear and RBF kernels achieved reasonable scores (95% AUC, 84% SE, and 88% SP and 96% AUC, 63% SE, and 99% SP respectively) as applied to the Mixed and Best-Radiomics groups respectively.

### **Classification-balanced cohort**

Similar to the analyses of the unbalanced cohort, another CV step followed by a validation step has been conducted on the balanced training and test cohorts including 32 and 16 subjects respectively. The results of the CV step are shown in *Table 8*. Here, as compared to the CV step for the unbalanced cohort, more consistent results are achieved. The highest scores (up to 99% AUC, 99% SE, and 99% SP) are achieved by almost all of the pairs of classifier-parameter groups. These extremely high scores are achieved by the grid search for the purpose of hyperparameter tuning and are not considered as final accuracies.

The results of the hyperparameter tuning for the balanced cohort are presented in *Table 9* and the results of applying the classifiers with the tuned parameters to the validation cohort are shown in *Table 10* and *Figure 3*. Here, except for the clinical parameters group which showed insufficient prediction accuracies, the linear, polynomial, and RBF kernel SVM classifiers showed the most consistent performances (91% AUC, 99% SE, and 62% SP for linear SVM on radiomics group, 88% AUC, 99% SE, and 62% SP for polynomial SVM on radiomics group, and 80% AUC, 75% SE, and 75% SP for RBF SVM on Best-Mixed group).

The final step was the permutation test which has resulted in a P value of 0.0043 that assures the significance of the results.

## **Discussion**

We showed that parameters of PSMA PET (Min and

**Table 5** Results of hyperparameter tuning step, applying 3-fold cross-validation (CV) for the unbalanced cohort: Prediction scores of the five ML classifiers on the five different feature or parameter groups on the unbalanced data-set of 56 subjects in the first CV step

Feature group	Radiomics	Clinical	Mixed	Best-radiomics
Classifier	AUC/SE/SP (%)	AUC/SE/SP (%)	AUC/SE/SP (%)	AUC/SE/SP (%)
Linear Kernel SVM	74/85/80	79/86/99	74/86/60	78/99/60
Polynomial Kernel SVM	74/92/99	79/93/80	74/85/99	78/99/67
RBF Kernel SVM	74/92/99	68/69/99	79/99/99	83/99/99
Extra Trees	84/92/67	84/93/83	89/92/83	84/99/80
Random Forest	79/92/60	84/93/67	84/92/67	79/99/60

AUC, area under the curve; SE, sensitivity; SP, specificity; SVM, support vector machine.

**Table 6** Results of hyperparameter tuning step, applying 3-fold cross-validation (CV) for the unbalanced cohort: Tuned hyperparameters of the five ML classifiers on the five different feature or parameter groups on the unbalanced data-set of 56 subjects in the first validation step

Feature group	Radiomics	Clinical	Mixed	Best-radiomics
Classifier	Tuned parameters	Tuned parameters	Tuned parameters	Tuned parameters
Linear Kernel SVM	C=2, gamma=0.001	C=1000, gamma=0.001	C=10, gamma=0.001	C=1, gamma=0.001
Polynomial Kernel SVM	C=1, degree=3	C=1, degree=3	C=1, degree=3	C=32768, degree=3
RBF Kernel SVM	C=1000, gamma=0.5	C=10, gamma=0.5	C=128, gamma=0.5	C=10, gamma=8
Extra Trees	max_depth=20, min_samples_leaf=10	max_depth=20, min_samples_leaf=10	max_depth=10, min_samples_leaf=8	max_depth=10, min_samples_leaf=10
Random Forest	max_depth=15, min_samples_leaf=10	max_depth=5, min_samples_leaf=4	max_depth=20, min_samples_leaf=8	max_depth=1, min_samples_leaf=10

SVM, support vector machine.

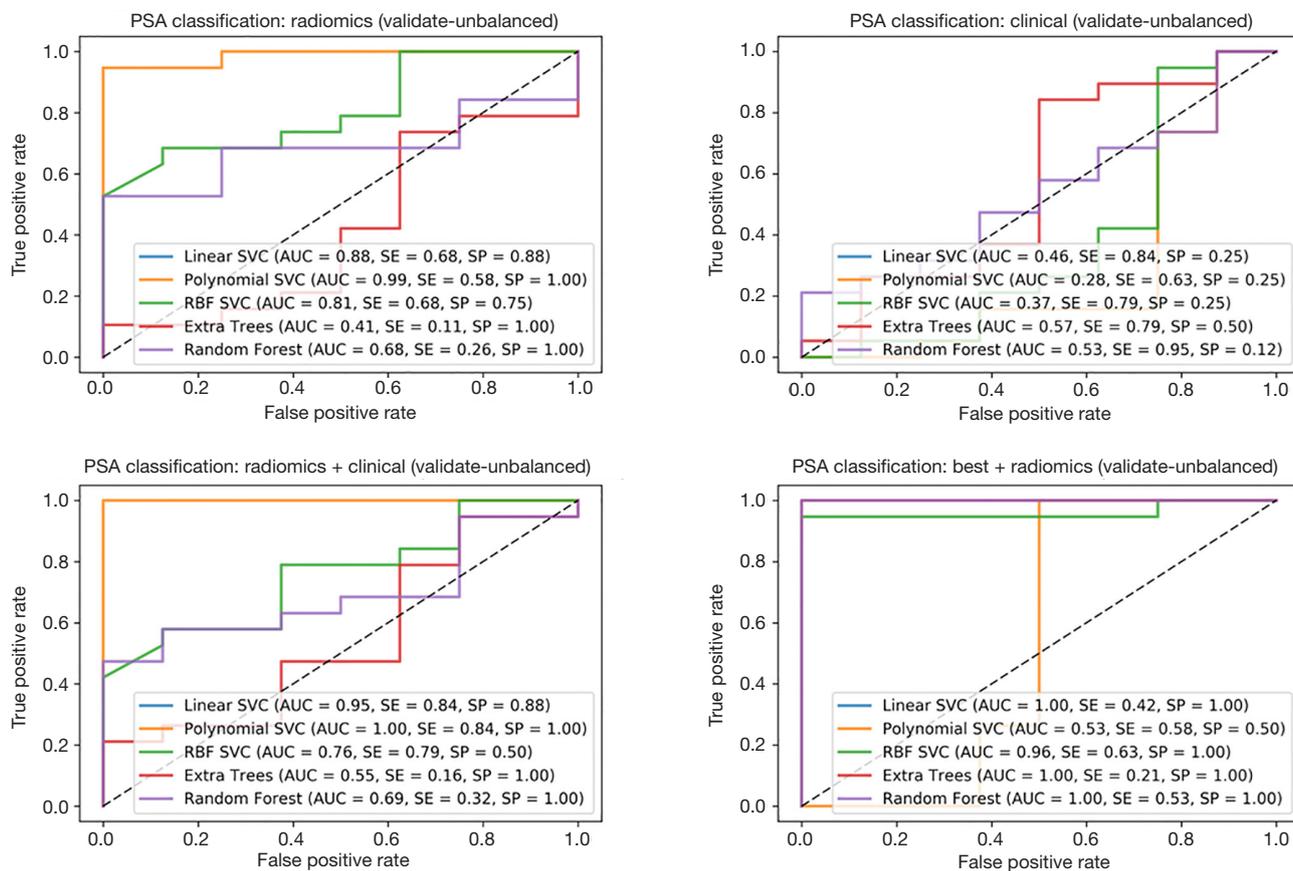
**Table 7** Results of validation step for the unbalanced cohort: prediction scores of the five ML classifiers on the five different feature or parameter groups on the unbalanced data-set of 56 subjects in the first validation step

Feature group	Radiomics	Clinical	Mixed	Best-radiomics
Classifier	AUC/SE/SP (%)	AUC/SE/SP (%)	AUC/SE/SP (%)	AUC/SE/SP (%)
Linear Kernel SVM	88/68/88	46/84/25	95/84/88	99/42/99
Polynomial Kernel SVM	99/58/99	28/63/25	99/84/99	53/58/50
RBF Kernel SVM	81/68/75	37/79/25	76/79/50	96/63/99
Extra Trees	41/11/99	57/79/50	55/16/99	99/21/99
Random Forest	68/26/99	53/95/12	69/32/99	99/53/99

ML, machine learning; AUC, area under the curve; SE, sensitivity; SP, specificity; SVM, support vector machine.

correlation) have statistically significant correlations with the PSA level difference as a surrogate marker for therapy response prediction, which is in accordance with the findings by Khurshid *et al.* (13). Furthermore, it was shown that some of the features from the low-dose CT (CT\_

Min, CT-Busyness, and CT-Coarseness) as well as three clinical parameters (Alp1, Time Difference, and Gleason score as defined in *Table 2*) have strong correlations with PSA level difference. In addition, by applying ML classifiers with tuned hyperparameters, we showed that features from



**Figure 2** Receiver operating characteristic (ROC) curves for the final validation step on the unbalanced data-set. The five different diagrams are for the four different feature groups (radiomics, clinical, radiomics and clinical, and best radiomics).

**Table 8** Results of hyperparameter tuning step, applying 3-fold cross-validation (CV) for the balanced cohort: Prediction scores of the five ML classifiers on the five different feature or parameter groups on the balanced data-set of 32 subjects in the second CV step

Feature group	Radiomics	Clinical	Mixed	Best-radiomics	Best-mixed
Classifier	AUC/SE/SP (%)	AUC/SE/SP (%)	AUC/SE/SP (%)	AUC/SE/SP (%)	AUC/SE/SP (%)
Linear Kernel SVM	90/99/99	91/99/99	99/99/99	90/99/80	99/99/99
Polynomial Kernel SVM	73/99/99	91/99/99	99/99/99	90/99/99	99/99/99
RBF Kernel SVM	90/80/99	99/99/99	99/99/99	90/99/99	99/99/99
Extra Trees	91/99/99	99/99/99	99/99/99	90/99/99	99/99/99
Random Forest	90/99/99	99/99/99	90/99/99	90/99/99	99/99/99

AUC, area under the curve; SE, sensitivity; SP, specificity; SVM, support vector machine.

baseline <sup>68</sup>Ga-PSMA scan can help to predict responders to <sup>177</sup>Lu-PSMA therapy with reasonable certainty.

Due to the retrospective characteristic of the study and because of the fortunate fact that most of the PC patients examined at our <sup>68</sup>Ga-PSMA PET/CT center are

responders to the <sup>177</sup>Lu-PSMA therapy, our original cohort was unbalanced with regard to response to the therapy. Thus, the whole cohort consisted of 59 responders and 24 non-responders. Although the unbalanced cohort achieved reasonable results in terms of prediction accuracies, similar

**Table 9** Results of hyperparameter tuning step, applying 3-Fold cross-validation (CV) for the balanced cohort: Tuned hyperparameters of the five ML classifiers on the five different feature or parameter groups on the balanced data-set of 32 subjects in the second validation step

Feature group	Radiomics	Clinical	Mixed	Best-radiomics	Best-mixed
Classifier	Tuned Parameters	Tuned Parameters	Tuned Parameters	Tuned Parameters	Tuned Parameters
Linear Kernel SVM	C=1, gamma=0.001	C=100, gamma=0.001	C=10, gamma=0.001	C=1, gamma=0.001	C=32,768, gamma=0.001
Polynomial Kernel SVM	C=1, degree=2	C=10, degree=3	C=10, degree=3	C=32,768, degree=3	C=10, degree=3
RBF Kernel SVM	C=1, gamma=2	C=10, gamma=2	C=1, gamma=0.03125	C=100, gamma=0.001	C=100, gamma=8
Extra Trees	max_depth=5, min_samples_leaf=10	max_depth=5, min_samples_leaf=4	max_depth=10, min_samples_leaf=10	max_depth=25, min_samples_leaf=10	max_depth=10, min_samples_leaf=10
Random Forest	max_depth=1, min_samples_leaf=10	max_depth=5, min_samples_leaf=10	max_depth=10, min_samples_leaf=8	max_depth=5, min_samples_leaf=10	max_depth=10, min_samples_leaf=10

SVM, support vector machine.

**Table 10** Results of validation step for the balanced cohort: Prediction scores of the five ML classifiers on the five different feature or parameter groups on the balanced data-set of 32 subjects in the second validation step

Feature group	Radiomics	Clinical	Mixed	Best-radiomics	Best-mixed
Classifier	AUC/SE/SP (%)	AUC/SE/SP (%)	AUC/SE/SP (%)	AUC/SE/SP (%)	AUC/SE/SP (%)
Linear Kernel SVM	91/99/62	56/62/50	77/99/62	69/99/38	69/75/50
Polynomial Kernel SVM	88/99/62	58/75/50	75/75/62	80/88/50	75/75/62
RBF Kernel SVM	89/99/50	53/75/50	80/75/62	67/99/38	80/75/75
Extra Trees	86/88/50	45/50/38	80/99/50	68/75/50	61/62/38
Random Forest	80/88/50	42/62/25	81/99/50	71/88/38	75/99/25

ML, machine learning; AUC, area under the curve; SE, sensitivity; SP, specificity; SVM, support vector machine.

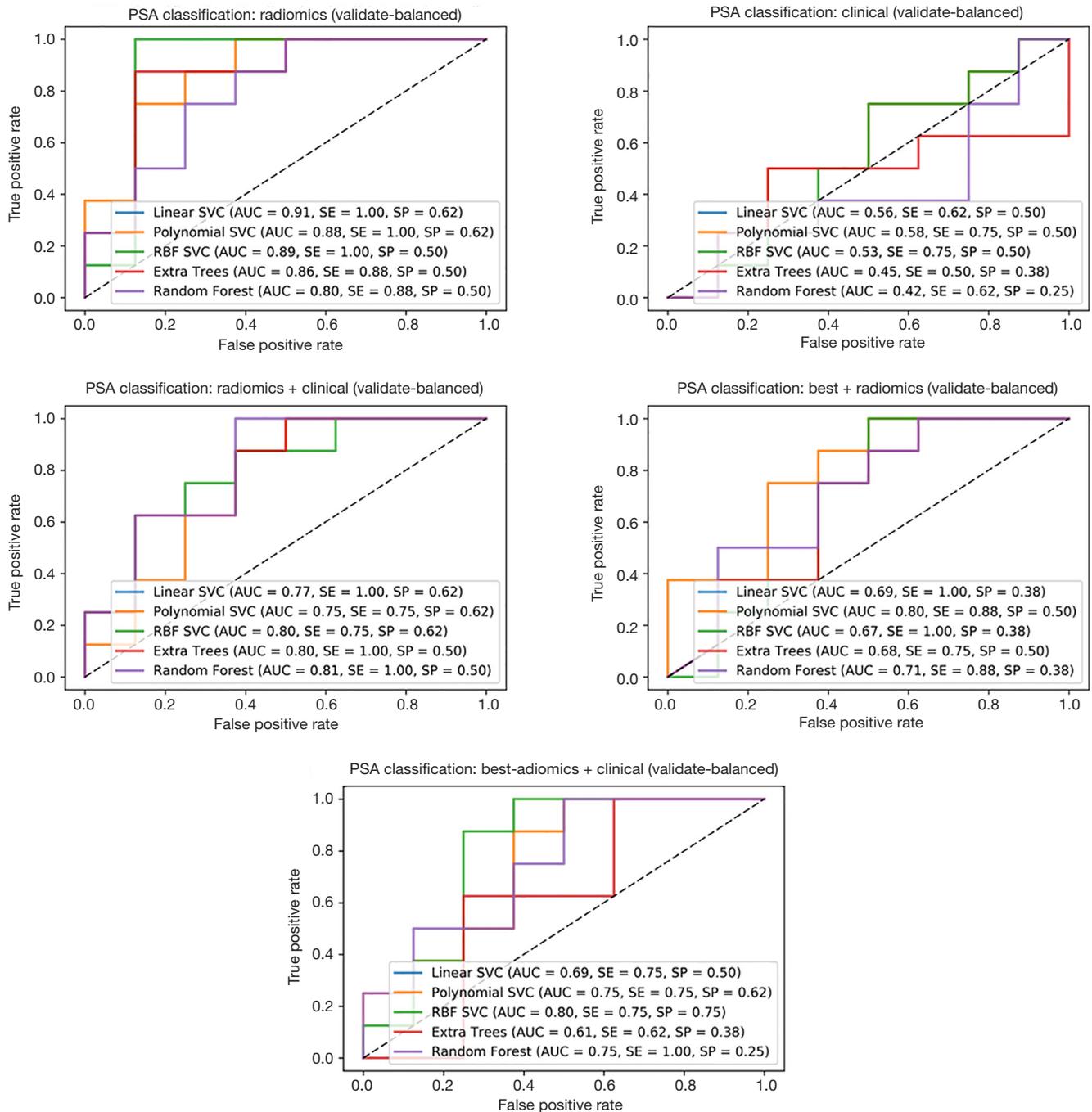
analyses were conducted on the balanced cohort to check if the accuracy scores could be maintained. However, as the size of the hold-out set for the balanced cohort (16 subjects) was relatively small, relatively low specificities were achieved in the corresponding validation step. This important observation urges for studies on bigger cohorts in the future.

Although the clinical parameters have shown insufficient prediction performances in the validation steps on balanced or unbalanced data-sets, however; the overall best accuracy scores (up to 80% AUC, 75% SE, and 75% SP) are achieved on the combination of best correlating radiomics features and clinical parameters with  $\Delta$ PSA (Best-Mixed) by SVM classifier with RBF kernel (Table 10).

As the results suggest, ML methods have shown their potential for further, automated algorithms for treatment response prediction in prostate cancer patients based on

$^{68}\text{Ga}$ -PSMA PET/CT data and therefore for decision-support tools. To implement this goal, our next steps include automated segmentation of hotspots, which was beyond the scope of this first study. Although in the presented study, the additional value of including clinical parameters could not be shown, in our opinion this is still an important topic and should be part of further studies.

Drawbacks of the study are for sure, that as gold-standard visual image analysis was used instead of histopathology as a real gold-standard. However, biopsies of more than one or two hotspots are hardly possible in patients, so this is actually the best option for ground truth data acquisition. Although we had just 83 patients included in this first study, we analyzed 2070 pathological hotspots in total, so that we could show statistical significance in our results. However, larger studies need to be performed in the future to enhance the predictive performances of the algorithms. Also beyond



**Figure 3** Receiver operating characteristic (ROC) curves for the final validation step on the balanced data-set. The five different diagrams are for the five different feature groups (radiomics, clinical, radiomics and clinical, best radiomics, and best mixed).

the scope of this study was the analysis of how the results can be applied on  $^{68}\text{Ga}$ -PSMA PET scans with different protocols [such as PET/MRI (23)] or obtained with other PET scanners (24). This is an important topic in this field and needs to be investigated in further studies.

## Conclusions

Machine learning based on pretherapeutic  $^{68}\text{Ga}$ -PSMA-PET/CT radiomics features has shown high potential to predict response to treatment with  $^{177}\text{Lu}$ -PSMA. The application of combination of best correlating radiomic features with PSA level change showed its superiority compared to clinical parameters for the treatment response prediction task.

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