Adding PSMA PET/CT to nomogram predicting extraprostatic extension of prostate cancer

Abbreviations

AUC	area under the curve
EPE	extraprostatic extension
Ga^{68}	Gallium 68
ISUP GG	International Society of Urological Pathology grade group
iv	intravenous
mpMRI	multi-parametric magnetic resonance imaging
MRI	magnetic resonance images
MRI P	magnetic resonance images prostate
PCa	prostate cancer
PI-RADS	Prostate Imaging Reporting and Data Systems
PSMA	prostate specific membrane antigen
PSMA PET/CT	prostate specific membrane antigen positron emission tomography/computed tomography
RP	radical prostatectomy
SUVmax	maximum standardized uptake value
TRUS	trans rectal ultrasound

Abstract

Introduction: Probability on extraprostatic extension of prostate cancer determines feasibility of a nerve-sparing radical prostatectomy. Multiple nomograms have been developed calculating probability of EPE. Research shows benefits of PSMA PET/CT scans concerning primary staging, but also suggest possible benefits concerning local staging. Can the maximal standardized uptake value (SUVmax) of the PSMA PET/CT improve predictions made by Santeon nomogram?

Materials & methods: A retrospective database consisting of 1400 patients diagnosed with prostate cancer patients was used. Patients with pre-operatively PSMA PET/CT and MRI prostate were extracted and analysed.

Results: 117 patients were included and 137 tumour positive sides were identified. EPE was present in 35% of sides and 53% of all cases were deemed T3 according to the MRI report. Multivariable regression analyses showed that SUVmax is a significant predictor combined with the MRI T stadium to predict extraprostatic extension (EPE) and improves the area under the curve.

Discussion: Cohort and number of events is small, therefore not all predictors could be included due to high degrees of freedom. Predictors deemed significant in other studies are not significant in this cohort, possibly due to small cohort. As SUVmax is significant opposed to other predictors it possesses a certain predictive value. Cases with non-visible tumours on PSMA PET/CT were not excluded and could possibly lower true predictive performance of variables.

Conclusion: The relation between SUVmax and EPE is significant and thus strongly suggests SUVmax could be valuable in predicting side-specific extraprostatic extension.

Introduction

Radical prostatectomy (RP) is, with about 2.785 operations each year in the Netherlands, the most applied curative treatment for prostatic cancer in the Netherlands.[1] The nerves running dorsally adjacent to the prostate along both sides are responsible for urinary continence and erectile function.[2] Therefore most frequently occurring complications after RP are incontinence and erectile dysfunction.[2] To minimize complications the (unilaterally) nerve-sparing RP was introduced in 1982.[3] Although it has clear beneficial effects on complications it caused increasingly positive surgical margins.[4] Therefore a consideration should be made between quality of life versus possible cancer recurrence.[4, 5]

When deciding to perform a nerve-sparing RP it is vital to correctly stage the tumour and thus assess the presence or absence of (one-sided) extraprostatic extension (EPE). When there is a risk on EPE it is advised by international guidelines to not perform a nerve-sparing RP.[6] Although magnetic resonance images (MRI) of the prostate supplies much needed information, its sensitivity regarding EPE is only 57%.[7] The low sensitivity regarding (unilateral) EPE complicates the decision to perform a (unilaterally) nerve-sparing RP.

Therefore, multiple nomograms have been developed over time to predict the presence of EPE such as the Memorial Sloan Kettering Cancer Center nomogram and the Partin tables.[8] When there is a low probability on EPE this decreases the likelihood of a positive surgical margin when performing a nerve-sparing RP. Most nomograms are not side-specific, although EPE is in 85% of the cases and thus nerves could possibly be spared on the side with low probability on EPE.[9] The externally validated nomogram for side-specific EPE developed by Soeterik et al. was the first to include the results of multi-parametric magnetic resonance images (mpMRI) to predict side-specific EPE and reached an area under the curve (AUC) of 0.77-0.83.[8]

Studies have shown that prostate specific membrane antigen (PSMA) is mostly expressed in prostatic tissue, but also in the salivary glands among others.[10] Compared to benign tissue expression of PSMA is elevated in cancerous prostatic tissue.[11] The prostate specific membrane antigen positron emission tomography/computed tomography scan (PSMA PET/CT) uses this quality. Patients are injected intravenously with radioactively labelled PSMA antibodies after which the activity is measured.[10]
The PSMA PET/CT is mainly used to detect lymph node metastases in patients with biochemical reoccurrence of prostate cancer (PCa). Its diagnostic value has been proven by research and is advised in the international PCa guideline.[6] The PSMA PET/CT demonstrated a higher sensitivity and accuracy to detect lymph node metastases compared to CT-abdomen and bone scintigraphy. Compared to mpMRI the PSMA PET/CT can also detect smaller lymph node metastases.[12-14]

Recently PSMA PET/CT turned out valuable in the primary staging of high-risk PCa.[15] The maximum standardized uptake value (SUVmax) of the PSMA PET/CT is found to have a correlation with the Gleason score as well as the existence of EPE.[16-20] An increasing number of articles suggest the PSMA PET/CT scan offers many benefits. Maybe the SUVmax could enhance the predictions made by the Santeon nomogram.[21]

Will the Santeon nomogram improve in predicting side-specific EPE with the addition of SUVmax from the PSMA PET/CT scan?

Patients and methods

Patient population and study data

A database consisting of 1400 patients diagnosed with PCa from 2014 until the end of 2020 at St. Antonius Hospital, Nieuwegein-Utrecht was searched for patients who had undergone a RP. Patients with a PSMA PET/CT scan and an MRI Prostate (MRI P) pre-operatively were extracted from this database. Most hospitals utilize a Gallium 68 (Ga^{68}) PSMA PET/CT scan, patients who received a PSMA PET/CT scan with a different tracer than Ga^{68} (Fluor 18 e.g.) were excluded to improve comparability between cases. Patients of whom the PSMA PET/CT scan was not fully assessable due to incorrect fusion of PSMA PET and CT results in the radiological viewer (SECTRA IDS7) were excluded.

Included patients were transcoded into sides with a visible tumour on either MRI P or PSMA PET/CT scan. In case of a lesion deemed centrally by the radiologist and when no other visible lesions were present the highest International Society of Urological Pathology grade group (ISUP GG), the highest MRI T classification and highest SUVmax of both sides was assigned. In presence of more lesions on one side the highest parameters were entered for the respective side. In case of a central lesion and a lesion in one of both sides the central lesion was reassessed and assigned to the side with the most tumour volume. Cases without a visible tumour were excluded to improve its comparability to regular clinical practice.

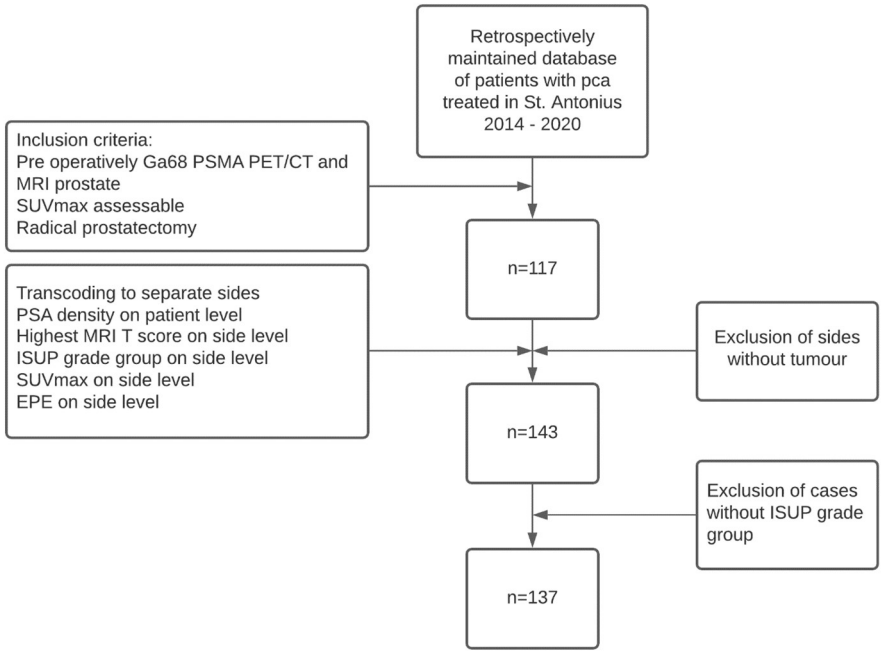

Figure 1: Flowchart

Predictor selection

Predictors used in the final nomogram by Soeterik et al. were documented in the exact same way; PSA density (PSAD) on a patient-based level.[8] Highest ISUP GG and highest MRI T classification were documented on a side-specific level.

Which parameter from the PSMA PET/CT to be used was selected by reviewing recent research as stated by Steyerberg et al.[22] According to multiple studies, SUVmax is associated with a higher ISUP GG of the actual tumour as well as adverse outcomes such as EPE or cancer reoccurrence.[13, 14, 16-18]

MRI protocol

A 3 Tesla MRI combined with a body coil was used. In most cases patients were administered Gadolinium (1mg/kg). Radiological reports were made by experienced radiologists with at least 2 years of experience with reporting on prostate MRI scans according to the Prostate Imaging Reporting and Data Systems (PI-RADS) version 2 guidelines and from 2019 onward the slightly modified PI-RADS version 2.1.[23, 24]

Ga^{68} PSMA PET/CT protocol

Patients are prepared by drinking 0.5L water in the two hours preceding the scan and at least 1L of water on the day of the scan. The patient is, if needed (dependent on location/machine), administered furosemide intravenously (iv). Ga^{68} PSMA dosage is established on weight and on the exact type of machine. After administration of Ga^{68} PSMA ligand iv, the intravenous system is flushed with 100ml NaCl and after 55 to 65 minutes the scan is made. After completion of the PET scan a low dose CT scan is made after which the images are combined. Due to different types of (PSMA PET) scanners the results, such as SUVmax, are corrected to guarantee their comparability.

Predictors and outcome definitions

Patient based PSA density was, if not given in the mpMRI report, calculated by using most recent pre-operatively measured PSA and, preferably, prostate volume in the MRI report or as measured by trans rectal ultrasound (TRUS). The mpMRI information was documented on a side-specific level and subdivided into three subclasses: nonvisible lesions (T1), organ-confined lesions (T2) and lesions with EPE (T3).

To assess the existence of EPE out of the MRI report, these were scoured for thickening or suspicion for invasion of the neurovascular bundle, bulging of the prostatic contour, capsule irregularity, or presence of a hypo intensive signal in a periprostatic area. In most MRI reports a T stadium (TNM) was also given out of which presence of EPE could mostly be deducted. Clear statements in the reports about EPE were scored accordingly. In less clear reports EPE was scored as being negative.

Highest ISUP GG was documented for both the right and left side separately.

SUVmax was documented side-specific and was taken over from the radiological report or by measuring it in the radiological viewer. Before measuring the SUVmax in the viewer, the author (S.v.S.) was trained by a nuclear medicine physician (J.L.), with over 5 years of experience with the PSMA PET/CT, to measure the SUVmax.

Histopathological information post-operatively including pathological tumour stage and highest ISUP GG found were documented for both sides separately. On presence of EPE the laterality was documented as well. EPE was determined histopathologically as a tumour bulging beyond the prostate contour, as a tumour blended in with periprostatic tissue or as a tumour between nerves of the neurovascular bundle. Microscopic bladder neck invasion and seminal vesicle invasion were not

considered EPE in this study, corresponding to the Santeon nomogram, since the existence of these parameters can depend on the method of cutting, among other things.[25]

Statistics

All information was collected in an online database by REDCap (version 10.6.19). All analyses have been done in SPSS Statistics 27.

To assess the relationship between a binary outcome (presence or absence of EPE) and independent predictors multiple binomial multivariate regression analyses have been done in SPSS on the acquired data. Important to know is if the predictor of interest has a significance value of 0.05 or less. This means in 95% of calculations the coefficient of the predictor is not zero and thus has influence on the outcome.[26] First the full model will be tested and if significant SUVmax will be added. If one or multiple predictors turn out to be insignificant, each will be removed and added to test if the predictor becomes or remain significant.

The rule of thumb concerning binomial multiple regression analysis determines there are 10 events per degree of freedom of the binary logistic model to not overfit the model.[27] Depending on the number of predictors and accordingly on the degrees of freedom it could be, for example, necessary to collapse predictors. The rule of thumb can be relaxed somewhat according to research by Vittinghoff et al.[28]

Another assumption of logistic regression states the necessity of a linear relationship between the variable and the logit of the outcome.[29] This assumption can be tested using the Box Tidwell test. Multiple solutions exist when this assumption is not met such as, but not limited to, including a squared term of the related predictor.[30, 31]

A third important assumption of logistic regression states there cannot be too much multicollinearity between predictors and Pearson's r coefficient should not be higher than 0.9.[32]

Significance is expressed two-tailed by default. When evidence shows that an increase of a predictor results in an increase of the probability on outcome and there is no evidence that a decrease of the predictor leads to a decrease in probability it is recommended to investigate the one-tailed significance and there halve the original output.[30]

Results

Patient population

In total, 117 patients were included, for baseline characteristics see figure 2. The included patients were transcoded in 143 cases and 7 were excluded due to missing ISUP GG. Missing ISUP GG could be explained in most cases due to receiving targeted biopsies on one side. Not all sides were missing ISUP GG at random; one patient did not consent to biopsies since he suffered from severe sepsis after biopsies years before. These cases with missing ISUP GG were excluded as can be seen in the flowchart (figure 1).

	N (%)
No. of patients	117
Age, median (IQR)	69 (64-72)
PSA (ng/mL), mean (SD)	14.74 (3,14-26,34)
PSA density (ng/mL/mL), mean (SD)	0.339 (0,06-0.636)
Clinical T stage	
T1c	46 (39)
T2	14 (12)
T2a	16 (14)
T2b	12 (10)
T2c	10 (9)
T3	18 (15)
Unknown	1 (1)
Radiological T stage	
T0	8 (7)
T2/T2a	45 (39)
T2b	3 (3)
T2c	10 (9)
T2/T3 (uncertain EPE)	2 (2)
T3a	40 (34)
T3b	7 (6)
T4	0 (0)
Unknown	2 (2) (Not described)
Biopsy type	
TRUS-guided systematic	41 (35)
MRI guided	6 (5)
TRUS + MRI guided	69 (59)
Missing	1 (1)
Pathological stage	
T2	42 (36)
T2a	1 (1)
T2b	0 (0)
T2c	16 (14)
T3a	36 (31)
T3b	22 (19)
T4	0 (0)

Figure 2: Baseline characteristics of included patients

After inclusion and exclusion 137 cases remained as can be seen in the flowchart in figure 1. When plotting SUVmax on MRI T stadium, SUVmax values turn out to be unevenly distributed. For this reason, the median value of SUVmax is used in figure 3. In this table SUVmax is grouped per MRI T stadium and on the absence or presence of EPE as seen by the pathologist. This table shows a noticeable difference of SUVmax between the MRI T groups whether EPE is present. From this table it is also clear the groups are small, specifically the group with EPE in the MRI T0 group consists of one side and that the group with EPE consists of 48 sides.

Descriptive statistics show 43% of the cases consist of ISUP GG 4 or higher and 24% are deemed clinically higher than T2. A clear indication there are many high-risk PCa cases.

MRI T classification	EPE		Total
	No	Yes	
T0	14 (93%)	1 (7%)	15 (11%)
SUVmax median	5,30	8,40	
T2	54 (75%)	18 (25%)	72 (53%)
SUVmax median	6,46	10,15	
T3	21 (42%)	29 (58%)	50 (36%)
SUVmax median	8,80	10,00	
Total	89 (65%)	48 (35%)	137

Figure 3: Median SUVmax grouped by EPE & by MRI T classification

Multivariable logistic regression

The predictors of choice add up to eight degrees of freedom and so eighty events should therefore be occurring instead of 48 in this cohort. To ensure a robust conclusion, the decision is made to collapse the MRI T0 and T2 group, since the T0 group is small. Attempting to further reduce degrees of freedom it turns out the benign group, both ISUP GG group 1 and 2 are small and therefore collapsed. Biopsy grade groups 4 and 5 are collapsed for that same reason as well. Ultimately resulting in four degrees of freedom for the model consisting of the collapsed MRI T stadium, PSAD and ISUP GG.

The development of the Santeon nomogram clearly indicated a significant and linear relationship between PSAD, MRI T and ISUP GG and the probability of EPE.

Applying the Box Tidwell test shows there is no linear relationship between the outcome and SUVmax. By plotting the probability of EPE against the SUVmax, however, it does show an almost linear curve as can be seen in figure 4, although the last data point clearly is not perfectly on the regression line.

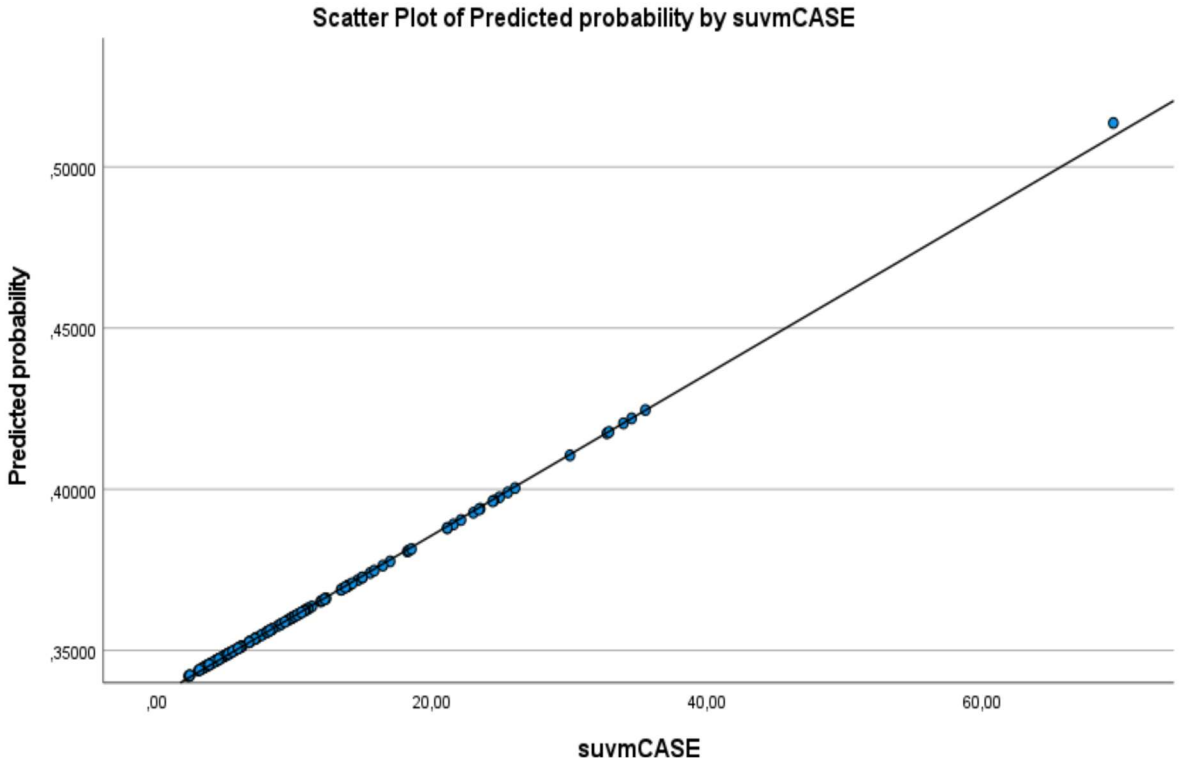

Figure 4: Scatterplot of SUVmax values on predicted probability with regression line.

A squared term is added to see if there is a curvilinear association. As it turns out this term increases significance of SUVmax, and both are significant as can be seen in figure 5. Thus, the conclusion is there is a slight concave curve in the linear relationship as can be deducted from the slightly negative coefficient of $SUVmax^2$ in combination with the regular term. To test if there is a cubic relationship, $SUVmax^3$ was added as well, but turned out to be insignificant.

	B	Sig.
SUVmax	0,229	0,010
$SUVmax^2$	-0,006	0,024
Constant	-2,031	<0,001

Figure 5: Regression analysis output where B is coefficient and Sig. is significance.

When testing for collinearity between each predictor individually, Pearson's r coefficient does not exceed the 0.7. Therefore, too much multicollinearity is not a problem.

After running a logistic regression with the collapsed predictors PSAD turns out to be insignificant, see figure 6.

	Sig.
PSA density	0,771
ISUP GG	0,100
MRI T	<0,001
Constant	-1,936

Figure 6: Regression analysis output where Sig. is significance.

After eliminating PSAD, ISUP GG becomes just insignificant with 0.052 and thus MRI T class is the one remaining significant predictor of the Santeon nomogram within this cohort. SUVmax and $SUVmax^2$ are added to the logistic regression model and turn out to be significant ($p<0.05$).
Part of the insignificance could possibly be explained by collapsing of the predictor. Running a multivariate logistic regression model with the uncollapsed ISUP GG and MRI T collapsed and vice versa shows the same conclusion; ISUP GG remains insignificant.

Since two predictors turn out to be significant there are less degrees of freedom and so the uncollapsed predictors can be used. SUVmax turns out to be insignificant with a p value of 0.055. With the removal of ISUP GG as a predictor, however, the six cases with missing ISUP GG (figure 1) can be included in the analysis as well, resulting in a total of 143 cases. Running a regression analysis among the 143 cases results in SUVmax to be significant with a p value <0.05.

Running a regression analysis again with the 143 cases using the uncollapsed MRI T stadium results in the parameters as can be seen in Figure 7. These parameters reflect a model's performance with multiple mathematical calculations. These values cannot be compared to different models or populations but can be used to compare the performance of nested models. Increasing parameters mean the model is performing better except for the ''-2 Log Likelihood''; a number closer to zero reflects

better performance. Running a new regression analysis with the addition of SUVmax results in improved model performance in all parameters as can be seen when comparing figure 7 to figure 8.

	Chi-square	Sig.	-2 Log likelihood	Cox & Snell R	Nagelkerke R
Model	21,109	<0,001	156,353	0,143	0,197

Figure 5: Regression analysis output where Sig. is significance.

	Chi-square	Sig.	-2 Log likelihood	Cox & Snell R	Nagelkerke R
Model	25,439	<0,001	152,023	0,169	0,233

Figure 5: Regression analysis output where Sig. is significance.

A different method of assessing model performance is by calculating the AUC of the receiver operating curve. The AUC of the model consisting of MRI T alone results in 0.707 (figure 9). After addition of SUVmax the AUC increases to 0.749 (figure 10), an increase of 5.94%.

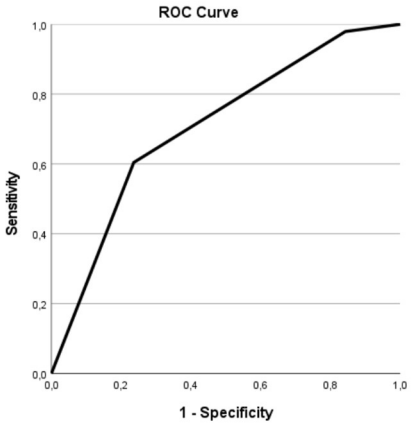

Figure 9: AUC of model with MRI T

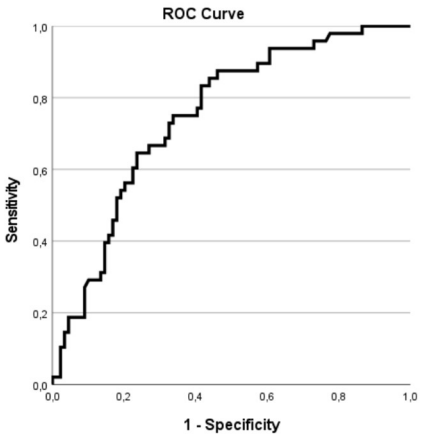

Figure 9: AUC of model with MRI T & SUVmax.

Discussion

The purpose of this study was to determine if adding the PSMA PET/CT scan could improve the Santeon nomogram in predicting side-specific EPE.[8] This study strongly suggests SUVmax could be a valuable parameter to predict side-specific EPE according to its significance in the performed regression analyses and the improved AUC. The predictive value of SUVmax is also illustrated, since it is significant in the performed regression analyses as opposed to ISUP GG and PSAD.

The fact SUVmax is the only significant predictor next to MRI T stadium could possibly be explained by a higher predictive value than PSAD and ISUP GG or the collapsing of both those predictors. It could also be explained by the characteristics of this specific cohort as it consists of mostly high-risk tumours, since PSMA PET/CT is mostly used for high-risk PCa. Another explanation could be found in the size of the cohort since it only consists of 117 patients. Other studies suggest a diagnostic or predictive value of SUVmax as well, in line with the findings of this study, however. [16-20, 33]

Multiple studies have shown clear benefits of the PSMA PET/CT scan to other imaging modalities such as MRI P in the primary staging of PCa, particularly concerning lymph node metastases as described in guidelines concerning PCa as well.[6, 12-14] It appears SUVmax and adverse outcomes, such as biochemical reoccurrence, and an unfavourable primary stage of the tumour seem to be very correlated.[16-20, 33] For instance, the group of Roberts et al. recently published a study describing a correlation between increasing SUVmax and primary stage as well as local staging, specifically among MRI staged T3 tumours. For local staging the PSMA PET/CT is described useful in the detection of PCa rather than up- or downgrading the MRI T stadium after retrospectively analysing 71 patients with more than sixty percent pathologically T3 tumours. The study emphasizes the found prognostic value PSMA PET/CT scans could have.[19] Little is known, however, about the potential diagnostic or predictive value of PSMA PET/CT scans concerning local staging as research on this topic is extremely scarce. The article by Bouchelouche et al. reviewing recent literature stated PSMA-based scan might improve sensitivity to detect extraprostatic PCa in line with Roberts et al.[18, 19] The review ends, however, by stating more research must be done to further assess the role PSMA PET/CT scans can play in the workflow concerning PCa. Different studies also describe additional benefits of the PSMA PET/CT scan such as finding clinically significant PCa after repeated negative biopsies despite a high suspicion.[34, 35]

However, no studies have been found at the time of writing this study, which focus on the exact role PSMA PET/CT scans can play in the local staging of PCa. Much remains unclear about the predictive value of SUVmax, but this study suggests there is, potentially, diagnostic value of SUVmax.

A strength of this study would be the exclusion of sides without a visible tumour as this better resembles clinical practice. The study data were collected from daily clinical practice and thus reflect realistic scenarios. Another strength can be found in substantiating known evidence about the hypothesis before statistics have been calculated which prove the hypothesis is probably correct. This study supplies new insights on using results of the PSMA PET/CT scan as there is little to no evidence to be found on this subject.

Limitations must be acknowledged as well. Analyses have been conducted on a small cohort reflected by the little number of events per MRI T group and in general. The impact the small size of the cohort has is also demonstrated since the addition of the six cases without ISUP GG results in significance of SUVmax as opposed to insignificance of SUVmax without those cases. The addition of these cases could introduce bias when ISUP GG is not missing at random, but for some other reason. Preferably the performance of the Santeon nomogram would be measured with all the predictors and compared to a full model including the SUVmax, unfortunately too few events were present. Insignificance of PSAD and ISUP GG could however possibly be attributed to the necessary collapsing of said predictors.[30] Data was collected from a single centre theorizing the possibility results found in this cohort could differ from other hospitals. PSMA PET/CT scanning is used increasingly over time, but usually remains applied for high risk PCa in general. Allocation bias could have been introduced by manual allocating side of the

lesion in case a central lesion as well as a unilateral lesion was present. Possibly EPE was only centrally located, but inadvertently the unilateral lesion was EPE positive due to the localization of the pathologist and the author. In six included cases no hotspot was visible on PSMA PET/CT. These cases could potentially obfuscate the true value of the SUVmax, since the median SUVmax of these cases was 3.1 whereas can be seen in figure 3 lowest SUVmax median is five or higher.

Preferably a larger cohort would be used in which ISUP GG and PSAD are significant corresponding to the Santeon nomogram to compare the model with all predictors of choice. Furthermore, the question remains if the same predictive value of SUVmax is also present in a larger cohort.

Conclusion

Taking everything into account this research indicates a potentially beneficial predictive value of SUVmax due to its significance and improved AUC. The question remains however if these results are also found in a larger cohort and when comparing models with more predictors. If SUVmax turns out to be a valuable predictor a better consideration can be made whether to perform a nerve-sparing RP. This finding could potentially lead to a better quality of life of PCa patients treated with surgery due to fewer RP's without (unilateral) nerve-sparing.[5]

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