research article

MRI and ^{11}C acetate PET/CT for prediction of regional lymph node metastasis in newly diagnosed prostate cancer

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Background. The aim of the study was to examine the value of quantitative and qualitative MRI and ^{11}C acetate PET/CT parameters in predicting regional lymph node (LN) metastasis of newly diagnosed prostate cancer (PCa).

Patients and methods. Patients with intermediate (n = 6) and high risk (n = 47) PCa underwent 3T MRI (40 patients) and ^{11}C acetate PET/CT (53 patients) before extended pelvic LN dissection. For each patient the visually most suspicious LN was assessed for mean apparent diffusion coefficient (ADCmean), maximal standardized uptake value (SUVmax), size and shape and the primary tumour for T stage on MRI and ADCmean and SUVmax in the index lesion. The variables were analysed in simple and multiple logistic regression analysis.

Results. All variables, except ADCmean and SUVmax of the primary tumor, were independent predictors of LN metastasis. In multiple logistic regression analysis the best model was ADCmean in combintion with MRI T-stage where both were independent predictors of LN metastasis, this combination had an AUC of 0.81 which was higher than the AUC of 0.65 for LN ADCmean alone and the AUC of 0.69 for MRI T-stage alone.

Conclusions. Several quantitative and qualitative imaging parameters are predictive of regional LN metastasis in PCa. The combination of ADCmean in lymph nodes and T-stage on MRI was the best model in multiple logistic regression with increased predictive value compared to lymph node ADCmean and T-stage on MRI alone.

Key words: prostatic neoplasm; lymph nodes; lymph node excision; diffusion magnetic resonance imaging; positron-emission tomography

Introduction

Detection of regional lymph node (LN) metastases in prostate cancer (PCa) is of great importance, as it is a prognosticator of significantly decreased disease-specific survival rates and biochemical recurrence-free rates.[1] Further correct identification of patients with lymph node metastases, might have important implications regarding the addition of adjuvant therapy.

Extended pelvic lymph node dissection (ePLND) is gold standard for diagnosing LN involvement in patients at increased risk of LN metastases.[2] An extended approach is recommended since limited dissection of the obturator fossa misses 50% of metastases.[3] However ePLND is associated with high cost, hospitalization and possibly post-operative complications. Hence imaging may have a role to select patients suitable for lymph node dissection.

Conventional imaging methods such as CT and MRI have limited value in the evaluation of LN metastases in patients with prostate cancer. Both techniques depend on morphological criteria, mainly size and shape of lymph nodes, which is the likely explanation to the low sensitivity of conventional CT and MRI.[4-6]

As morphological criteria not are sufficient, functional imaging techniques have received increased attention in the scientific literature. Diffusion weighted (DWI) MRI has been studied by several researchers[7-12] as well as ^{11}C and ^{18}F Choline PET/CT.[13-16] There are a few publications on lymph node staging in PCa with the PET radiotracer ^{11}C acetate.[17,18] Acetate can be metabolized in different ways, the most important in PCa is the fatty acid synthase pathway (FAS), as this pathway is overexpressed in PCa.[19-21] The uptake of this tracer can be measured semi-quantitatively by the standardized uptake value (SUV).

DWI depicts the motion of water molecules within tissues, a process that is restricted in highly cellular tissues, for example malignant tumors. Apparent diffusion coefficient (ADC) value is a quantitative parameter of DWI.[22] A few studies have indicated that ADC measurements can differentiate malignant prostate lesions from benign prostatic tissue, however with a significant overlap.[23-25]

The aim of this study was to examine the value of quantitative and qualitative MRI and ^{11}C acetate PET/CT parameters in predicting regional lymph node metastasis of newly diagnosed prostate cancer of intermediate and high risk, with histopathology from ePLND as reference standard

Patients and methods

Patients

Between July 2010 and June 2013, 53 consecutive patients with intermediate- (n = 6) and high-risk (n = 47) prostate cancer according to D´Amico risk categories[26] were prospectively included. All patients underwent imaging within two weeks before ePLND, 40 had 3T MRI DWI and ^{11}C acetate PET/CT, the remaining 13 had ^{11}C acetate PET/CT only. Inclusion criteria were a negative bone scintigraphy and a risk of LN spread of >20% according to the Briganti nomogram.[27] Exclusion criteria were contraindication to laparascopy, contraindication to MRI examination (*e.g.*, pacemaker, magnetic implants) and hip replacement or previous hip or lower pelvis fractures. The study was approved by the regional ethics and radiation ethics committees. Informed consent was obtained in all patients before participation.

All patients in our study have been included in two previous studies[11,18] that focused on non-quantitative validation of MRI DWI and ^{11}C acetate PET/CT.

MRI and ^{11}C acetate PET/CT

Both examinations were performed within the same day.

Patients were measured with a 3 Tesla scanner (Achieva, Philips Medical Systems, Best, The Netherlands) using a two-channel whole body coil for excitation and a six-element phase-array coil for receiving. MRI from apex of the prostate to the aortic bifurcation was performed using T_1- (T1W) and T_2-weighted (T2W) turbo spin echo (TSE) sequences in axial plane. The main T1W acquisition parameters were as follows: Repetition time/Echo time (TR/TE), 670/10 ms; field of view (FOV) 260 x 260 mm^2; acquisition matrix 150 x 186; number of signal averages (NSA), 2. T2W TSE scans were acquired with TR/TE 7000/120 ms; FOV 260 x 260 mm^2; acquisition matrix 166 x 173; NSA, 2. Axial fat suppressed diffusion weighted imaging (DWI) was performed using the spin-echo single-shot echo-planar imaging (SE-EPI) technique (TR/TE, 2450/55 ms; FOV 220 x 280 mm^2; acquisition matrix 73 x 94; diffusion encoding gradients b = 0, 100, 200, 400, 500 s/mm^2; NSA, 3). The apparent diffusion coefficient (ADC) maps were obtained with mono-exponential fitting. Separate DWI imaging with single b value (1000 s/mm^2) was performed for qualitative diagnostics

Axial T1W (TR/TE, 500/8 ms) and T2W TSE (TR/TE, 3000/100 ms) images of the prostate gland and vesicles were obtained with FOV 160 × 160 and acquisition matrix 182 x 200 and 160 x 200, respectively. NSA = 3 for both acquisitions. Axial DWI/ADC SE-EPI scans used following parameters: TR/TE, 1800/55 ms; FOV, 220×220 mm^2; acquisition matrix 98 x 126; NSA, 4; diffusion encoding gradients b = 0, 100, 200, 400, 500 s/mm^2. The apparent diffusion coefficient (ADC) maps were obtained with mono-exponential fitting Separate DWI imaging with single b value (1000 s/mm^2) was performed for qualitative diagnostics.

^{11}C acetate was synthesized according to in-house good manufacturing practice (GMP) procedures. Patients were fasted for at least 4 hours prior to PET. Five MBq/kg body weight of ^{11}C acetate was injected intravenously in an antecubital vein 10 min prior to PET acquisition. PET/CT was per-

formed on a GE Discovery ST16 (GE Healthcare, Waukesha, ML) hybrid scanner. A venous phase contrast-enhanced low dose CT used both for morphologic analysis and for attenuation correction (140 kV, auto-mA 10-80 mA), and PET with 3 min per bed position, covering regions from the upper thighs to the neck, typically obtained in 6 bed positions. Total PET acquisition time was 18 min. Total effective dose of both PET and CT with this protocol was approx. 9 mSv. PET images were corrected for attenuation, dead-time, scatter and decay, and reconstructed to a 50 cm field of view in a 128 x 128 matrix using an iterative reconstruction algorithm with 2 iterations and 21 subsets as supplied by the manufacturer.

Surgical technique

A systematic laparoscopic extended lymph node dissection was performed first from the external and common iliac artery and vein from the ureter and to the deep circumflex vein, respecting the genitofemoral nerve, secondly from the obturator fossa, meaning the space between the external iliac vein down to the obturator nerve and lastly the internal iliac area from the obturator nerve down to internal iliac artery and to the deep pelvic floor. The specimen were separated in 3 fractions from each side and sent to the pathologist.

Histopathological evaluation

The specimens were fixed in 4% buffered formaldehyde. Lymph nodes smaller than 10 mm were embedded whole. Larger lymph nodes were dissected longitudinally through the hilum or cut serially at 3 mm intervals depending on the size. The specimens were dehydrated in alcohol for 21 hours. Thereafter embedded in paraffin and sectioned (4 μm) at two levels. Sections were stained with haematoxylin and eosin. For each patient the presence and the number of LN metastases were reported. Immunohistochemistry with pan-cytokeratin was used when necessary to confirm a minor metastasis.

MRI and ^{11}C acetate PET/CT analysis

A specialized radiologist (C.v.B) with more than ten years experience in nuclear medicine and oncological radiology, blinded to histopathology results and clinical information, analysed the images using Carestream Vue PACS with built in PET/CT as software (Carestream Health, Inc, Rochester, NY, USA). At least 6 months passed between the non quantitative analysis of this material, previous published[11,18] and the quantitative analysis in the present manuscript.

MRI and ^{11}C acetate PET/CT were reviewed side by side, the lymph node with the visually most suspicious findings with regard to diffusion restriction, PET activity, shape and size, were chosen from any of the the anatomical regions included in a ePLND, for each patient. Diffusion restriction and PET activity weighed heavily in the selection of the visually most suspicious LN, secondly LN shape and thirdly LN size. In case of normal LN findings, the largest LN was assessed. The chosen lymph nodes were assessed for the following features; SUVmax measured by placing a region of interest (ROI) encompassing the uptake, the maximum pixel value representing SUVmax, ADCmean measured by placing a ROI within the LN contour in the lymph nodes largest axial section, size was measured in the lymph nodes short axis and LN shape was registered as oval or round. MRI DWI was also analysed for primary tumour T stage; obvious extra-capsular extension was registered as MRI-T3a, obvious spread to seminal vesicles was registered as MRI-T3b, if non of this features were present the T stage was registered as ≤ MRI-T2. The index lesion, *i.e.* the largest lesion, in the primary tumour was also assessed, tumour-SUVmax and tumour-ADCmean were measured by the same method described for LNs above.

Statistics

Receiver operating curve (ROC) analysis of LN-ADCmean, LN-SUVmax, LN size, tumour-ADCmean and tumour-SUVmax was performed to determine optimal cut-off from which the variables were dichotomized. Variables were then analysed in simple logistic regression analysis to determine their significance. Different combinations of the significant variables in the simple analysis were then included in multiple logistic regression models but the number of observations in each variable did not allow us to use more than two variables at the same time. For each model the predicted values were compared with the observed values, area under the curve (AUC), sensitivity, specificity, positive and negative predictive value (PPV, NPV), accuracy, pseudo R^2 (Nagelkerke) and Hosmer-Lemeshow statistic were calculated to determine their classification performance. Multicollinearity between variables, was measured with Cramer´s V.

A p-value less than 0.05 was considered statistically significant. Statistical analysis was performed with Dell Inc. (2015). Dell Statistica (data analysis software system), version 13. software.dell.com.

Results

The patients´ clinical characteristics are outlined in Table 1. Of the 53 patients included in the study 26 (49%) had LN metastases at ePLND. Among the 40 patients that had 3T MRI DWI plus ^{11}C acetate PET/CT 50% had LN metastasis, patient characteristics for this subset of patients has previously been described.[11] The variables MRI-T-stage, LN-ADCmean and tumour-ADCmean had 40 observations, the remaining variables tumour-SUVmax, LN-SUVmax, LN-size and LN-shape had 53 observations. The smallest LN in the material was 3.8 mm, the median ROI size for ADC measurements in LN´s was 42 mm^2 with range 16–334 mm^2, the ROI size for ADC measurements in primary tumour was ≥ 80 mm^2 (Table 2).

The ROC analysis of Tumour-ADCmean and Tumour-SUVmax showed insufficient classification with AUC of 0.53 and 0.49 respectively. For LN-SUVmax, LN-ADCmean and LN-size the corresponding AUC were 0.69, 0.72 and 0.62 respectively, these variables were dichotomized using optimal thresholds calculated from the ROC curve and included in simple logistic regression along with MRI-T-stage and LN-shape (Table 3). ROC determined threshold values are presented in Table 3. All variables included in simple logistic regression analysis were significant predictors of LN metastasis and therefore included in multiple logistic regressions models in combination of two (Table 4). Ten combinations were calculated and in model one to three both variables appeared as independent predictors of LN metastasis: LN-ADCmean in combination with LN-SUVmax, LN-shape and MRI-T-stage, respectively, where the best combinations for prediction of LN metastasis (Table 4). Model three (LN-ADCmean and MRI-T-stage) was the model with highest AUC and pseudo R^2, 0.81 and 0.39 respectively, which was higher than the AUC of 0.65 and pseudo R^2 of 0.12 for LN-ADCmean alone and the AUC of 0.69 and pseudo R^2 of 0.17 for MRI-T-stage alone

In model one to three both variables were significant, multicollinearity between the predictors were weak, Cramers´V of 0.09, 0.15 and 0.16 respectively. This in combination with adequate goodness of fit show the validity of the models.

TABLE 1. Patient characteristics

Patient characteristics	
Patients, *n*	53
Age, median (range)	68 (55–76)
LN positive patients, *n*	26
PSA level ng/ml, mean (median, range)	24 (19, 3–112)
Biopsy Gleason score, *n* (%)	
6	5 (9.4)
7	39 (73.6)
8	5 (9.4)
9	4 (7.5)
D´Amico risk classification, *n* (%)	
Intermediate	6 (11.3)
High	47 (88.7)
Clincal T-stage, *n* (%)	
T1c	1 (1.9)
T2	11 (20.8)
T3	41 (77.4)
Risk of LN invasion*, *n*	
19–59%	27
≥ 60%	26

LN = lymph node; * Calculated according to Briganti nomogram (26)

TABLE 2. Investigational findings at MRI DWI and ^{11}C Acetate PET/CT

MRI DWI and ^{11}C Acetate PET/CT findings	
LN-ADCmean 10^{-6} mm^2 /s, mean (SD) range	917 (191) 582–1398
LN-SUVmax, mean (SD) range	1.8 (1.2) 0.7–5.9
LN size mm, mean (SD) range	6.6 (3.7) 3.8–28.3
Proportion of LNs with round shape, *n*	19
Proportion of LNs with oval shape, *n*	34
MRI T-stage, *n*	
< T3	25
T3a	14
T3b	14
LN ADC Roi size mm^2, median (range)	42 (16–334)
Tumor ADC Roi size mm^2	≥ 80

ADC = Apparent diffusion coefficient b0-b500; LN = lymph node; MRI T-stage: determined with MRI, only clear cut cases were reported as T3a and T3b; ROI = Region of interest; SUV = Standardized uptake value

Discussion

Our prospective study of predominantly high risk PCa patients undergoing ePLND for LN staging,

TABLE 3. MRI DWI and [11]C Acetate PET/CT variables dichotomized using ROC curve and analyzed with simple logistic regression

	N0 *n*	N1 *n*	OR	95%CI	p-value	Threshold	AUC	Pseudo R²*	Sensitivity/Specificity/PPV/NPV
LN-ADCmean 10^{-6} mm² /s	21	19	3.6	1.1-11.6	0.031	≤ 800	0.65	0.12	58/**73**/**76**/53
LN-SUVmax	28	25	5.4	1.6-18.7	0.008	≥ 1.6	0.68	0.18	72/68/52/83
LN-size mm	28	25	8.7	1.7–44.9	0.010	≥ 7.9	0.66	**0.20**	**83**/63/40/**93**
LN round shape	5	14	5.9	1.7-20.4	0.006		**0.69**	**0.20**	74/68/56/82
LN oval shape	23	11	ref	ref	ref	ref	ref	ref	ref
MRI-T-stage									
≤ T2	18	7	ref	ref	ref	ref	ref	ref	ref
T3a	7	7	2.00	0.4-10.5	0.412				
T3b	3	11	6.0	1.2-29.4	0.027		**0.69**	0.17	65/67/65/67

* Nagelkerke´s R²; ADC = Apparent Diffusion Coefficient b0-b500; AUC = Area Under the Curve; CI = Confidence Interval; LN: lymph node; MRI T-stage: determined with MRI, only clear cut cases were reported as T3a and T3b; N0 = No lymph node metastases at ePLND (extended lymph node resection); N1 = Verified lymph node metastases at ePLND; NPV = Negative Predictive Value; OR = Odds Ratio; PPV = Positive Predictive Value; SUV = Standardized uptake value; Treshold calculated with ROC analysis; Bold numbers indicate highest values

show that a quantitative and qualitative analysis of LN and primary tumor findings at MRI DWI and [11]C acetate PET/CT can provide a range of single and combined parameters to help radiologists evaluating the probability of regional LN metastases. LN-ADCmean, LN-SUVmax and LN-size were significant predictors of LN metastases as were lymph node with round shape and stage T3b at MRI, while Tumour-ADCmean and Tumour-SUVmax had insufficient classification properties. In multiple logistic regression analysis the best combination was LN-ADCmean and MRI-T-stage

TABLE 4. MRI DWI and [11]C Acetate PET/CT variables dichotomized with ROC curve and analyzed with multiple logistic regression

Model*	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
LN-ADCmean 10^{-6} mm² /s	3.7 (1.1–13.3), 0.040	4.1 (1.1–14.7), 0.032	8.4 (1.8–39.0), 0.007	2.7 (0.8–9.5), 0.110						
LN-SUVmax	5.6 (1.5–20.6), 0.010				2.7 (0.6–11.1), 0.179	4.7 (1.1–20.5), 0.040	2.3 (0.5–10.7), 0.30			
LN-shape		5.7 (1.5–21.2), 0.010			3.7 (0.9–15.0), 0.069			6.2 (1.4–27.2), 0.016	2.8 (0.5–14.7), 0.226	
MRI T-stage T3b[a] / ≤ T2			6.8 (1.1–41.6), 0.039			5.3 (1.0–28.6), 0.051		3.9 (0.7–22.0), 0.126		4.5 (0.8–25.2), 0.083
LN-size mm				7.5 (1.4–40.3), 0.018			4.8 (0.7–34.7), 0.116)		3.8 (0.4–31.6), 0.224	9.3 (1.4–61.1), 0.020
[c]Psedo R²	0.27	0.30	**0.39**	0.26	0.24	0.29	0.22	0.33	0.23	0.34
AUC	0.75	0.76	**0.81**	0.73	0.71	0.75	0.68	0.79	0.71	0.75
Sensitivity	72	74	67	**83**	63	65	68	74	74	74
Specificity	68	68	77	65	66	72	65	**83**	68	73
PPV	52	56	80	40	60	75	52	**85**	56	70
NPV	83	82	62	**93**	68	62	79	71	82	76
Cramers´V[b]	0.09	0.15	0.16	0.25	0.54	0.28	0.66	0.37	0.72	0.34
Accuracy	69	70	71	69	64	68	66	**78**	70	73

* Model one through ten: presented with OR (95%CI), p-value. [a] T3a is not presented in the table, this is because it is not significant in any of the ten models above. [b] Multicollinearity; [c] Nagel-kerke´s R²; AUC = Area Under the Curve; CI = Confidence Interval; LN = lymph node; MRI T-stage: only clear cut cases were reported as T3b, Apparent Diffusion Coefficient b0-b500, NPV = Negative Predictive Value; OR = Odds Ratio; PPV = Positive Predictive Value; SUV = Standardized uptake value; Bold numbers indicate highest values

(model three), this combination increased the predictive value compared to that of each parameter alone. To the best or our knowledge this is the first study investigating quantitative and qualitative predictors of regional LN metastases from MRI and ^{11}C acetate PET/CT, in patients with a risk of LN spread of >20% according to the Briganti nomogram[27] with histopathology as reference standard.

One article, which combines quantitative and qualitative analysis of 11C acetate PET/CT and MRI for diagnostic analysis or suspected prostate cancer, has previously been published.[28] However, in that study they included both patients with suspected and verified prostate cancer and analysed the combined imaging modalities to determine diagnostic accuracy for both local and distant staging, including only 15 patients with histopathological lymph node verification. Eleven of these 15 patients were found to have positive regional lymph nodes giving a sensitivity, specificity, and diagnostic accuracy for multiparametric MRI of 72.7%, 100%, and 95%, respectively, *i.e.* better than our results. They also found that multiparametric [11C]-acetate PET-MRI further improved the diagnostic accuracy for detection of regional lymph node metastases compared with MRI and PET alone. This is similar to our results that LN-ADCmean in combination with LN-SUVmax, LN-shape and MRI-T-stage, respectively, where the best combinations and significant predictors of LN metastasis.

A recent retrospective study by Park *et al.*[29] investigated 101 PCa patients, with normal sized lymph nodes, undergoing ePLND with MRI DWI at 3T. In simple logistic regression PSA, Gleason score, greatest percentage of biopsy core, percentage of positive cores, ADC of index lesion in prostate gland and MRI T stage were all independent predictors of regional LN metastasis. In multiple analyses only MRI T stage was significant. This finding is similar to our study since MRI-T-stage is a strong predictor in our material. A limitation of the study by Park *et al.* is that only 9 patients had LN metastasis, whereas 92 patients did not, this makes the logistic regression model unbalanced.

Another recent study by Batra *et al.*[30] investigated predictive factors for LN metastases in 100 patients undergoing ePLND. Variables examined in simple logistic regression analysis were PSA, Gleason score, clinical stage, D'Amico risk category and features of locally advanced disease on MRI (defined as extraprostatic extension, seminal vesicle invasion and enlarged pelvic lymph nodes). Clinical stage and features of locally advanced disease were predictive of LN metastases. In multiple logistic regression clinical stage only was predictive of LN metastases.

These results are not directly comparable to ours since all but 2 patients in the study by Batra *et al.* had clinically localized disease, whereas the majority of patients in our study (77.4%) had T3 disease. Further the definition of locally advanced disease included findings of enlarged pelvic lymph nodes, while in our study MRI-T-stage was defined by T stage on MRI. A disadvantage of the study by Batra *et al.* is that only 17% of the included patients had N1 disease.

Recently ^{68}Ga-PSMA PET/CT became apparent as a promising new tracer binding to the prostate specific membrane antigen (PSMA). A few studies have evaluated the diagnostic performance of this tracer, in lymph node staging at initial diagnosis of PCa, with ePLND as reference standard.[30-32] Sensitivity ranged from 61% to 82% and specificity from 84% to 95% in these studies. The sensitivity of ^{68}Ga-PSMA PET/CT is higher, but specificity is somewhat lower, compared to ^{11}C acetate PET/CT.[18]

The ADC value is largely dependent on the diffusion weighting factors (b values) used in the protocol, variability of the ADC value of up to 40% has been described with the use of different b values.[34] To a lesser degree, ADC values can differ between MRI systems.[35] This explains why cut-offs for ADC values cited in the literature vary greatly. For example in our study the lymph node ADCmean cut-off obtained with ROC curve analysis was 800 x 10^{-6} mm^2/s, based on the b values 0,100, 200, 400, 500. In another study the cut-off of the ADCmean value was 910 x 10^{-6} mm^2/s based on b values 500, 800, 1000 and 1500.[12] In three studies with the following b values 50, 300, 600, the reported pelvic lymph node ADC mean cut-off were 1430 x 10^{-6} mm^2/s, 1010 10^{-6} mm^2/s and 1300 10^{-6} mm^2/s respectively.[7,9,10] There is clearly a need for standardization of DWI acquisitions to enable comparisons of ADC values between reports.[36]

Up to 80% of regional LN metastases in PCa are located in normal sized lymph nodes[36], it is therefore unavoidable to measure ADC in normal sized lymph nodes when evaluating DWI in nodal staging of PCa. This is reflected by the ADC ROI size of pelvic lymph nodes in our study ranging from 16-334 mm^2 with median size of 42 mm^2. In a study by Thoeny *et al.*[38] investigating normal sized pelvic lymph nodes in bladder cancer and PCa, the ADC ROI size ranged from 2.8-40.7 mm^2. Obviously there is a risk of partial volume effect when measuring ADC in small lymph nodes. However, Eiber *et al.*[9] showed that measurements of the ADC value

are not substantially distorted by partial volume effects even in lymph nodes down to 6 mm.

The ROC curve analysis optimal cut-off for LN size short axis diameter was 7.9 mm in our study, this is similar to the cut-off of 8 mm for LN size that has been reported in two previous studies of pelvic nodes in PCa.[7,9] Regarding optimal cut-off for lymph node SUVmax in ^{11}C acetate PET/CT, there are no previous publications to compare with.

Interestingly, we could show that lymph nodes with round shape were predictive of metastases, which is confirming its position in general interpretation criteria of CT and MRI imaging in PCa. Regarding the multiple logistic regression analysis, one can argue that the combination of LN-shape and MRI-T-stage (model eight) had AUC and pseudo R^2 close to model three (LN-ADCmean and MRI-T-stage) and even higher accuracy 0.78 *vs*. 0.71 compared to model three. However only LN-shape in mode eight appeared as independent predictor. LN-ADCmean and LN-SUVmax were independent predictors in model one as were LN-ADCmean in combination with LN-shape in model two, however not reaching the results in model three.

It should be noted that all of the predictive factors in our study except LN-SUVmax can be obtained from non-contrast enhanced MRI, this is of relevance since ^{11}C acetate PET/CT is associated with high cost and limited availability. However the LN for measurement of ADC values was also chosen according to ^{11}C acetate PET/CT uptake, and this might bias the interpretation.

A limitation of this study is that the number of observations did not allow for more than two variables in multiple logistic regression analysis, which prevented us from exploring the true diagnostic performance of a large model with all predictors included. Another limitation is that the ADC measurements in lymph nodes smaller than 6 mm could be hampered by partial volume effect. Since it is very difficult to correlate single, specific lymph node histology to imaging, we chose to select the lymph node with the visually most suspicious findings from any of the anatomical regions included in the ePLND, for each patient.

Conclusions

In this prospective study we could show that a number of predictive factors for regional lymph node metastasis in patients with intermediate- and high-risk PCa could be retrieved from MRI and ^{11}C acetate PET/CT. SUVmax, ADCmean, size and shape of regional lymph nodes were all predictive of lymph node metastases as were T-stage on MRI. The combination of ADCmean in lymph nodes and T-stage on MRI was the best model in multiple logistic regression with increased predictive value compared to lymph node ADCmean and T-stage on MRI alone. The relatively low diagnostic accuracy in the present study, as well as in other previously published studies[10,32], show that there is at present a limited role of anatomical and functional imaging for lymph node staging in patients with prostate cancer. Future studies including more patients are needed to validate our findings.

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