The sensitivity of $[^{11}C]$choline PET/CT to localize prostate cancer depends on the tumor configuration.

Michael Souvatzoglou$^1$, Gregor Weirich$^2$, Sarah Schwarzenboeck$^1$, Tobias Maurer$^3$, Tibor Schuster$^4$, Ralph Alexander Bundschuh$^1$, Matthias Eiber$^5$, Ken Herrmann$^1$, Hubert Kuebler$^3$, Hans Juergen Wester$^1$, Heinz Hoefler$^2$, Juergen Gschwend$^3$, Markus Schwaiger$^1$, Uwe Treiber$^3$, Bernd Joachim Krause$^1$

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Key words: $[^{11}C]$choline, PET/CT, prostate cancer, benign prostate hyperplasia

Corresponding author:
Michael Souvatzoglou
Nuklearmedizinische Klinik und Poliklinik der Technischen Universität München
Ismaninger Str. 22
81675 München
Germany
e mail: msouvatz@yahoo.de

1. Department of Nuclear Medicine, Technische Universität München
2. Institute of Pathology, Technische Universität München
3. Department of Urology, Technische Universität München
4. Institute of Epidemiology and Statistics, Technische Universität München
5. Department of Radiology, Technische Universität München

* Both authors contributed equally to this work
† Both authors contributed equally to this work as senior authors
Translational Relevance

An accurate non-invasive detection and localization of primary prostate cancer (PCa) is desirable as a substantial number of false negative biopsies in men with elevated PSA is reported. Functional/molecular imaging with PET/CT can image processes of tumor biology, often with higher accuracy compared to morphological imaging alone. However, conflicting results have been published recently concerning the ability of PET/CT with radiolabeled choline to detect and localize primary PCa. This study, comparing respective transaxial $[^{11}C]$choline-PET/CT and histopathology slices obtained from patients with biopsy proven PCa, contributes to this debate by evaluating a variety of factors possibly influencing tumor prediction. Further, it takes into account the influence of factors such as partial volume effect and spillover. $[^{11}C]$choline-PET/CT was not able to detect and localize prostate cancer accurately due to the intraprostatic tumor configuration and the not distinguishable choline uptake in PCa compared to benign prostate hyperplasia. This finding has some clinical implication as $[^{11}C]$choline-PET/CT can not be considered as a first line tool to diagnose PCa in men at risk.
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Abstract

Purpose:
To evaluate the dependency of the sensitivity of $[^{11}\text{C}]$choline-PET/CT for detecting and localising primary prostate cancer (PCa) on tumor configuration in the histologic specimen.

Experimental Design:
Fourty three patients with biopsy proven PCa were included. They underwent radical prostatectomy within 31 days after $[^{11}\text{C}]$choline-PET/CT. The transaxial image slices as well as the histologic specimens were analyzed by comparing the respective slices. $S_{\text{Vmax}}$ was calculated in each segment and correlated with histopathology respectively. The tumor configuration in the histologic specimen was grouped as: I=unifocal, II=multifocal, III=rind-like, IV=size<5mm. Data analysis included the investigation of detection of PCa by $S_{\text{Vmax}}$, the assessment of the influence of potential contributing factors on tumor prediction, and the evaluation if SUV could discriminate cancer tissue from BPH, prostatitis, HGPIN or normal prostate tissue.

For statistical analysis general estimation equation models were used.

Results:
Tumor configuration in histology was classified as I in 21, as II in 9, as III in 5 and as IV in 8 pts. The prostate segment involved by cancer is identified in 79% of the patients. $S_{\text{Vmax}}$ was located in the same side of the prostate in 95% of patients. Tumor configuration was the only factor significantly negatively influencing tumor prediction ($p<0.001$). PCa-$S_{\text{Vmax}}$ (median $S_{\text{Vmax}}=4.9$) was not significantly different from BPH-$S_{\text{Vmax}}$ (median $S_{\text{Vmax}}=4.5$) and prostatitis-$S_{\text{Vmax}}$ (median $S_{\text{Vmax}}=3.9$) $p=0.102$ and $p=0.054$ respectively.
Conclusion:

The detection and localization of PCa in the prostate with $[^{11}]C$-choline-PET/CT is impaired by tumor configuration. Additionally, in our patient population, PCa tissue could not be distinguished from benign pathologies in the prostate.
Prostate cancer (PCa) is currently the highest prevalent form of cancer in men (192,280 cases, 25% of all incident cases) and constitutes the second most common cause of cancer deaths (9%) in the USA (1, 2). The definite diagnosis depends on the presence of PCa in prostate biopsy cores. Unfortunately the false negative detection rate for transrectal ultrasound (TRUS) guided biopsies is exceeding 20%, resulting in repeated biopsies in high risk patients and in a lasting uncertainty in those patients about the cause of the PSA elevation (3).

Therefore, a diagnostic modality being able to accurately detect and localize PCa in the prostate would be desirable. Differences in the biologic behaviour of PCa and other non-malignant conditions that affect the prostate, such as prostatitis and benign prostate hyperplasia (BPH) are important considerations in the approach to imaging. Imaging modalities like CT, conventional MRI and TRUS have shown limited accuracy for the diagnosis and staging of primary prostate cancer. (4-8). Therefore a major challenge for imaging undetected local PCa is to increase diagnostic performance.

In recent years, positron emission tomography/computed tomography (PET/CT) has been introduced that combines functional and morphological data and allows for whole-body imaging. For molecular imaging with PET/CT, a high tumor to non-tumor uptake ratio in the prostate is a prerequisite for a PET-tracer used for diagnosis of primary PCa. As PET with $[^{18}\text{F}]$FDG has a limited sensitivity for imaging prostate cancer (9, 10) the choline metabolic pathway has been suggested to be a promising imaging target for PCa (11-15). While there is good agreement among several centers on the utility of PET/CT with $[^{11}\text{C}]$choline for the detection of
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recurrent disease after radical prostatectomy in patients with biochemical failure, controversies exist about the accuracy of this technique with respect to the primary detection of PCa. In PET and PET/CT studies that related $[^{11}C]$choline maximum standardized uptake values (SUV$_{\text{max}}$) within different prostate regions to the presence of cancer cells in the correspondent sextans either supported (16,17) or did not support (18,19) the use of radiolabeled choline to accurately localize primary PCa. Among several factors, tumor configuration has been discussed as a confounding factor impairing the diagnostic accuracy of $[^{11}C]$choline PET/CT. Therefore, we tested the hypothesis that the diagnostic accuracy of $[^{11}C]$choline PET/CT to localize prostate cancer depends on the tumor configuration.

Materials and Methods

Patients

Fourty-three consecutive patients (median age: 66, range: 50-76 years) with biopsy proven, untreated PCa were included in this study. Time between biopsy and $[^{11}C]$choline PET/CT had to be at least 15 days to be included in the study. All patients underwent standardized radical prostatectomy and pelvic lymph node dissection within 31 days (median: 6.0, range: 1 - 31 days) after $[^{11}C]$choline PET/CT. In this study we focus on the detection of PCa within the prostate using histopathology as gold standard. The median time interval between biopsy and PET/CT scan was 34.5 days (range: 15-117 days). The study was approved by the ethics committee. All patients provided informed consent for participation in the study. Patients who had proven concomitant cancer were not included in the study.
Synthesis of $[^{11}C]$choline

$[^{11}C]$choline was synthesized according to the method of Pascali et al. (20) with minor modifications. $[^{11}C]$choline was produced with radiochemical yields of 80-90%, based on $[^{11}C]$MeI, and radiochemical purity of >99%.

Imaging protocol:

Patients fasted at least 6 hours before $[^{11}C]$choline-PET/CT scanning. Five minutes after injection of 682±75 MBq $[^{11}C]$choline, patients underwent $[^{11}C]$choline-PET/CT (mid thigh – thorax) on a Sensation 16 Biograph PET/CT scanner (Siemens). The acquisition protocol included sequentially a low-dose CT (26 mAs, 120 kV, 0.5s per rotation, 5mm slice thickness) for attenuation correction, followed by the PET scan and a diagnostic CT in portal venous phase 80 seconds after i.v. injection of contrast agent (Imeron 300) (240 mAs, 120 kV, 0.5 s per rotation 5 mm slice thickness). All patients received a rectal filling with a negative contrast agent (100 – 150 ml). All PET scans were acquired in 3D mode with an acquisition time of 3 minutes per bed position. Transaxial and axial resolution using a ramp filter are 6.3 and 6.5mm in FWHM respectively (21). Emission data were corrected for randoms, dead time, scatter and attenuation and were reconstructed iteratively by an ordered-subsets expectation maximization algorithm (4 iterations, 8 subsets) followed by a post-reconstruction smoothing Gaussian filter (5 mm full width at half maximum).

Image analysis

Images were analyzed by two experienced nuclear medicine physicians and a doctoral student simultaneously, all of them being blinded to the pathology results. For image analysis the transaxial PET slices and the corresponding fused low dose-
CT slices were used. Latter were applied to determine the delineation of the organ contour, helping the matching with histology. Corresponding to the histopathological evaluation, a sextant based analysis of the images was performed using a grid, which was placed on each transaxial slice of the prostate. The first slice evaluated was always the one following the image in which the base of the prostate first appeared. Each prostate slice, except of the first and the last slice evaluated, were divided by the grid into 12 segments, 6 central and 6 peripheral segments (segmental model A, figure 1). The first and the last slice of each patient’s prostate were divided in 6 segments. The grid was adapted to each slice. To allow an assessment of the amount of tracer uptake we evaluated the $[^{11}\text{C}]$choline uptake by semiquantitative analysis. To minimize influence of the partial volume effect a, complementary, second analysis was performed in which two consecutive axial slices were added in one, and the segments of the right and left prostate site in those slices were added together, creating one segment for each side of the prostate in every slice (segmental model B). In each segment of these analyses a ROI was placed and the maximum standardized uptake value (SUV$_{\text{max}}$) was calculated.

In order to exclude a potential excretion of the tracer in the bladder as a factor confounding the results, the number of patients exhibiting $[^{11}\text{C}]$choline activity in the bladder was evaluated.

Volumetry of the prostate was performed on the diagnostic CT using a software (Volume; Siemens Healthcare) that implements a semiautomatic segmentation algorithm for volume measurements. The user defines a ROI around each axial slice of the prostate and sets a lower and an upper threshold (we chose 5HU and 1000 HU respectively). The algorithm creates a volume of interest. All voxels in
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the volume of interest with HU values between the lower and upper threshold are used for calculating the final volume (22).

Pathology

The analysis was performed by a board certified surgical pathologist with a ten years experience in urologic pathology (mainly prostate). He was blinded to the image results.

After surgical resection, the prostate gland was prepared for histological evaluation in a way that histopathological evaluation could be corresponded to the transaxial PET/CT images: The orientation of the prostate was preserved by inking right and left margins with different colors, by anatomical landmarks and by the different extensions of the prostate slices. After coating with india ink for definition of the resection status (R-status) and for laterality and fixation in 10% buffered formalin whole mount axial cross sections were obtained at 5mm intervals transversely in a plane perpendicular to the long axis of the gland in cranio-caudal direction (base - apex), in order to match the corresponding axial PET/CT slices. A 4µm whole-mount section from each slice was then stained with haematoxylin and eosin according to standard procedures. The sections were divided in 12 segments by applying and adjusting the same grid used for the evaluation of the PET/CT images. The presence and location of cancer foci, high-grade prostate intraepithelial neoplasm (HGPIN), prostatitis, and BPH were determined by the pathologist for each sextant. Additionally the predominant tumor configuration in the histologic specimen was classified in 4 groups: I= unifocal larger than 5mm (large unifocal), II= multifocal, III= rind-like shaped, IV= size<5mm. Tumors were staged according to the classification system of
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the International Union Against Cancer (UICC) 2004, and graded according to the Gleason score system.

Data analysis

Data analysis included the following:

1. The detection of PCa by SUV\textsubscript{max} was investigated. For this purpose the location of the SUV\textsubscript{max} of the whole prostate was assessed and compared to histopathology findings. SUV\textsubscript{max} was considered as being located in tumor tissue if the tumor site in histopathology was present in the same segment of the prostate within one section. Additionally, we looked for if the SUV\textsubscript{max} was located in the same side (right or left lobe) of the prostate as the tumor in histopathology.

2. The number of cases in which the SUV\textsubscript{max} was in a segment adjacent to a segment demonstrating cancer cells in histopathology was determined.

3. Furthermore, we evaluated if SUV\textsubscript{max} was influenced by T-stage, PSA level and Gleason score.

4. The influence of potential confounding factors such as tumor configuration, T stage, PSA and Gleason score on tumor prediction was assessed.

5. We evaluated if the SUV enables to discriminate cancer tissue from BPH, prostatitis, HGPIN or normal prostate tissue.

Statistical analysis

Generalized estimation equation (GEE) models (23) were used to assess the explanatory capability of SUV\textsubscript{max} for tumor prediction under consideration of tumor
Running title: Choline PET/CT PCa localization depends on tumor configuration configuration, T stage, PSA level and Gleason score and the ability to discriminate cancer tissue from BPH, prostatitis and HGPIN in the model. The GEE approach properly reflects the structure of repeated data and takes into account correlation of several segments per individual. Spearman correlation coefficient (rho) was used to quantify bivariate relationship of quantitative data and to assess statistical significance of monotonous dependencies (test for trend).

In order to correct for potential increment of false significant results by increased number of hypothesis formal tested, Bonferroni correction of p-values was applied in multiple comparisons. All statistical tests were conducted two-sided and (corrected) p-values less than 0.05 were considered to indicate statistical significance.

Results

Histopathology confirmed T2 (37/43; 86%) or T3 (6/43; 14%) prostate cancer in all patients. The tumors were classified according to their configuration in histology as I in 21, as II in 9, as III in 5 and as IV in 8 patients (figure 2). Median PSA value at the time of the PET/CT scan was 6.8 ng/ml (range: 1.0-38.7 ng/ml), median Gleason score was 6 (range 5-9, table 1). Four patients had lymph node metastases, one lymph node metastasis each. For more detailed information (TNM stage, size of the metastatic lymph nodes etc.) concerning these patients please see table 2. [11C]choline PET/CT suggested nodal metastasis in one of these patients (pt. No 4 in table 2). Overall patients, [11C]choline PET/CT showed evidence of distant metastases in 2/43 patients, both in bone, one in the first lumbal vertebral body and one in the right acetabulum respectively.
Median volume of the studied prostate glands was 62 ml (range: 30 ml – 132 ml). In segmental model A, each inner segment included approximately 2 – 4 voxels, each outer segment approximately 4 – 9 voxels, voxel volume is 0.14 ml.

Overall, in segmental model A, 2,526 segments were analyzed, with a median of 60 segments/patient (range: 30 - 96 segments/patient). PCa tissue was present in 602/2,526 (23.8%), BPH in 1,820/2,526 (72%), prostatitis in 576/2,526 (22.8%) and HGPIN in 149/2,526 (5.9%). In 21/149 (14%) segments HGPIN was concomitant with PCa, in 34/149 (23%) with BPH, in 63/149 (42%) with PCa and BPH, in 2/149 (1%) with prostatitis, in 9/149 (6%) with PCa and prostatitis, in 12/149 (8%) with BPH and prostatitis, 2/149 (1%) segments solely contained HGPIN and in 6/149 (4%) segments all four entities were present.

The median SUV\textsubscript{max} for all segments was 4.5 (range: 1.4-18.4).

Tumor detection by SUV\textsubscript{max}

SUV\textsubscript{max} was located in the same side of the prostate (right or left) in 41/43 (95%) of the patients. The two patients in whom SUV\textsubscript{max} was not ipsilateral to the tumor were both staged as T\textsubscript{2} and classified as IV (small tumors) and III (rind-like shaped) respectively.

Overall patients, SUV\textsubscript{max} was not significantly associated with PSA (rho = 0.099; p=0.526) or Gleason score (test for trend: p = 0.29, figure 3a and 3b). SUV in PCa tissue was significantly higher in T\textsubscript{3} staged tumors (median SUV\textsubscript{max}: 6.2, range: 2.5 – 18.4) compared to T\textsubscript{2} staged tumors (median SUV\textsubscript{max}: 4.3, range: 1.4 – 10.2; p = 0.013).
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Segmental model A

The area with the highest choline uptake in the prostate did not correspond to a segment involved with prostate cancer in 15/43 (35%) of the patients. \( \text{SUV}_{\text{max}} \) was located in a segment adjacent to a segment involved with prostate cancer in 7/15 patients.

Segmental model B

Overall, through segmental model B, 214 segments were partied with a median of 4 segments/patient (range: 4 - 8 segments/patient). Applying segmental model B, the area with the highest choline uptake in the prostate did not correspond to a segment involved with prostate cancer in 9/43 (21%) of the patients. All of those patients had cancers staged as T2. \( \text{SUV}_{\text{max}} \) was not located in PCa in 7/8 classified as IV (small tumors), 1/5 classified as III (rind-like shaped) and in 1/9 classified as II (multifocal) in the histologic specimen. \( \text{SUV}_{\text{max}} \) was located in PCa in all tumors (21/21) classified as I (large unifocal) in the histologic specimen.

In 4/43 patients moderate \([^{11}\text{C}]\text{choline}}\) uptake in the bladder was observed. However, \( \text{SUV} \) was not higher in the segments closer to the bladder. In three of those four patients, two having tumors classified as I and one as II, \( \text{SUV}_{\text{max}} \) was located in the segment involved with prostate cancer. In all three cases those were not segments neighbouring the bladder. In one patient (tumor classified as IV). \( \text{SUV}_{\text{max}} \) was not in the segment involved with prostate cancer and also not in a segment neighbouring the bladder.

Factors influencing tumor localization by PET
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Tumors classified as IV were significantly less accurately predicted compared to tumors classified as I (p < 0.001, table 3). T stage, PSA and Gleason score did not significantly influence tumor prediction (p = 0.24, p = 0.26, p = 0.18 respectively, table 3). For the results of this analysis concerning segmental model A please see table 3.

Discrimination of entities

For assessing if the different intraprostatic pathologies can be discriminated by the SUV, segments containing only one of the entities were taken into account. Solely PCa was observed in 86 segments, solely BPH in 1,004 and solely prostatitis in 95 segments. Solely HGPIN was observed in two segments and was therefore excluded from further analysis. In 454 segments solely normal prostate tissue was observed. For $SUV_{\text{max}}$ of the different entities see table 4. After correction for multiple comparisons $SUV_{\text{max}}$ in segments containing solely PCa tissue was significantly higher than in segments containing normal prostate tissue (p = 0.012) but there was no significant difference when compared to segments containing prostatitis or BPH (p = 0.054 and p = 0.102 respectively). Segments containing BPH had a significant higher $SUV_{\text{max}}$ than segments containing normal prostate tissue (p = 0.042). There was no significant difference between segments containing BPH and those containing prostatitis or between segments containing prostatitis and those containing normal prostate tissue (p > 0.99 respectively).

Discussion
The results of this study indicate that prostate cancer can not be accurately detected by $[^{11}\text{C}]$choline PET/CT. SUV$_{\text{max}}$ of the prostate was not located in PCa in 21% of patients. The lack of sensitivity of $[^{11}\text{C}]$choline PET/CT to diagnose primary prostate cancer is related to the inability to detect small tumors. Furthermore a multivariable analysis failed to demonstrate that $[^{11}\text{C}]$choline PET/CT can disentangle cancer tissue from benign entities, particularly from BPH, which is due to just minor differences in SUV-levels of the entities.

Initial studies utilizing $[^{11}\text{C}]$- or $[^{18}\text{F}]$-labeled choline derivates and PET reported encouraging results for detection of primary prostate cancer (17, 24). Further, Reske et al. in a study including 26 patients with biopsy proven PCa, comparing on a segment basis respective transaxial $[^{11}\text{C}]$choline PET/CT and histopathology slices, concluded, that major territories with PCa can be imaged precisely, located and differentiated from benign tissue with $[^{11}\text{C}]$choline PET/CT (16). In contrast, other groups reported on substantially lower sensitivities for $[^{11}\text{C}]$choline PET/CT to diagnose primary PCa (Farsad et al. 66%; Martorana et al. 66%, Giovacchini et al. 72%) (18, 25, 26).

Due to the limited spatial resolution of the scanner and the low number of voxels included in the segments, results are likely to be influenced by the partial volume effect and spillover. There is evidence for such an influence in our study as - using segmental model A - prostate cancer cells were located in an adjacent segment to the segment exhibiting the highest activity in 7/15 patients in whom PCa could not be localized by SUV$_{\text{max}}$. Therefore, segmental model B, that divided the prostate in substantially larger segments compared to segmental model A, is more appropriate for comparison with histopathology.
Another potential limitation is spillover from activity in the bladder. $[^{11}C]$choline is mainly not excreted renaly. However, moderate activity in the bladder has been observed (27). Concerning our study, as PCa could be localized correctly in three of the four patients who exhibited some $[^{11}C]$choline excretion in the bladder and SUV$_{\text{max}}$ was not located in segments closer to the bladder in any of the four patients, there was no substantial influence of bladder activity in localizing prostate cancer.

Discrepant results in different studies, may be partly due to differences in the patient populations studied. In order to enable comparability, we discuss the results of segmental model A to outline the differences. BPH was present in 72% of segments in our study, in part of them mixed with other entities, 40% of segments contained solely BPH tissue. In the patient population Reske et al studied a presence of BPH mixed with other entities in 48% of segments is reported, while 16% of segments contained solely BPH tissue (16). Farsad et al. reported a diffuse and constant presence of BPH in almost all prostatic regions of their studied patients, making them to omit on a distinct analysis concerning the differentiation of PCa from BPH (18). We omitted an attempt for visual analysis of the images because we observed diffuse intense uptake in the prostate of most patients and lack of a circumscribable focal uptake in many of them. Comparison with histopathology revealed, that this was due to the widespread presence of BPH in our patient population. Interestingly the entity being more difficult to be differentiated from PCa in our study was BPH, while SUV$_{\text{max}}$ of segments with prostatitis had a tendency to be lower in comparison to SUV$_{\text{max}}$ of segments with PCa. Our result, that SUV$_{\text{max}}$ of segments with PCa was not significantly different from SUV$_{\text{max}}$ of segments with prostatitis and significantly different when compared to segments with normal prostate tissue, could be due to the
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relatively low number of segments with prostatitis compared to segments with normal prostate tissue. $[^{11}C]$choline uptake in prostatitis was numerically lower than the uptake of normal prostate and demonstrated the same standard deviation. A higher SUV in prostatitis than in normal tissue could be expected. This was not the case in our study, and apart of the relatively low number of segments with prostatitis, low floridity of the inflammation could be considered. Our results yielding the inability of $[^{11}C]$choline PET/CT to differentiate PCa from benign prostatic pathologies are in line with the study of Martorana et al (25).

Concerning laterality, $[^{11}C]$choline PET/CT correctly localized the tumor in 95% of the patients, suggesting that it could be of help in men at risk of having PCa indicated by chronically elevated PSA levels, but experiencing repeated negative biopsies. However as only men with biopsy proven PCa have been included in our study, further studies are needed to evaluate this potential indication. Concerning the 4/43 patients with lymph node metastases, $[^{11}C]$choline PET/CT suggested nodal metastatic disease in one. The failure to detect the metastases, can be attributed to the small size of the involved lymph nodes in at least two of the three patients with a false negative scan.

Similar to previous studies no significant differences were observed when the SUV was related to PSA or to Gleason score (16, 18, 26, 28), while other groups reported of significant correlation between SUV and PSA level (24, 25). One of the potential utilities of $[^{11}C]$choline PET/CT in primary prostate cancer could be to identify patients with more aggressive lesions to avoid sampling error and appropriately direct therapy for higher grade, riskier tumors. The lack of correlation of uptake with PSA and Gleason score, indicates that $[^{11}C]$choline PET/CT is unlikely to identify those tumors accurately. However, patients included in this study had tumors
Considering that, a definite conclusion on whether $[^{11}C]$choline PET/CT can provide this information can not be drawn by our study.

SUV was significantly higher in T3 than in T2 tumors in our study. This is in line with Reske et al (16). Notably patients with T3 or T4 tumors represented a higher fraction in the patient population of that study (10/26; 38%) compared to the respective fraction in the present study (6/43; 14%), giving an additional hint about differences in the patient populations included. The low number of patients with T3 tumors included and the fact that the tumors of the patients included were of relatively lower grade could, in part, explain the detection inefficiency of $[^{11}C]$choline PET/CT in our study. However, our study indicates, concerning the widespread appearance of BPH in our patient population, exhibiting an uptake that can not be distinguished from the uptake of PCa, that detection inefficiency of $[^{11}C]$choline PET/CT is not restricted to small sized tumors but is additionally hampered by the presence of concomitant benign disease, in particular of BPH.

Our study has limitations, which affect all studies comparing corresponding transaxial $[^{11}C]$choline PET/CT and histopathologic slices. The accuracy of the correlation of findings in respective slices is limited due to image fusion, prostate shrinkage ex–vivo due to fixation, tissue distortion generated by the whole prostate step sections (cutting) and a potential sampling error because of the different slice thickness of the two methods (5mm vs. 4μm).

A further potential limitation is that $[^{11}C]$choline PET/CT was performed after prostate biopsy. Although we did not include patients who had undergone a biopsy shorter than 15 days prior to the PET/CT scan, we can not exclude that reparative changes after biopsy might have caused false positive $[^{11}C]$choline uptake. These may
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no longer be apparent on histopathologic examination as surgery was performed several days later.

Additionally, the precision of the activity measurement in tumors is limited by the partial volume effect and the spillover of activity from neighbouring segments. We analyzed and minimized the influence of such factors potentially confounding the results. We excluded spillover from the bladder.

Conclusion

The detection and localization of prostate cancer in the prostate with $[^{11}C]$choline-PET/CT is affected by tumor configuration. Small tumors can not be visualized. Additionally, in our patient population, PCa tissue could not be distinguished from benign pathologies in the prostate, particularly not from BPH. Therefore, our data do not support the routine use of PET/CT with $[^{11}C]$choline as a first-line screening procedure for prostate cancer in men at risk. A potential application of $[^{11}C]$choline PET/CT may be to increase the detection rate of cancer on repeated biopsies in patients who have a persistently high risk of prostate cancer and who have undergone multiple, iterative TRUS-guided biopsies with negative findings.
Figure legends

Figure 1
Illustration of segmental analysis (segmental model A). In column A, axial slices of low dose CT (I), PET (II) and fused PET/CT (III) images are shown with the grid overlaid. In column B is the corresponded histopathologic slice, with the grid overlaid and the segments numbered.

Figure 2
Histology specimen (A), PET/CT fused image (B) and PET image (C) of the respective slices in the four (I-IV) different tumor configuration forms observed. The tumor is outlined in the histologic specimen. In the first and in the second row unifocal (form I) and multifocal (form II) prostate cancer is shown respectively exhibiting intense $[^{11}C]$choline uptake ($\text{SUV}_{\text{max}} = 5.6$ in I and $\text{SUV}_{\text{max}} = 7.1$ in II). In the third and the fourth row prostate cancer with a rind-like shaped growth pattern (form III) and a small sized focus of cancer (form IV) are shown respectively, that are not visualized in the corresponding PET images ($\text{SUV}_{\text{max}} = 5.7$ located in benign prostate hyperplasia in III and $\text{SUV}_{\text{max}} = 3.5$ located in normal prostate tissue in IV).

Figure 3a
Scatter plot of PSA and SUVmax indicating the lack of correlation between the two values (Spearman correlation coefficient $\rho = 0.099$; $p=0.526$).

Figure 3b
Scatter plot between Gleason score and SUVmax indicating that the two values were not associated (test for trend: $p = 0.29$).
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References


Nuklearmedizin 2006;45: 126-33.


## Table 1

Patient characteristics, tumor configuration and $\text{SUV}_{\text{max}}$ localization of the respective cancers

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<tr>
<td>(segmental model B)</td>
<td>no</td>
<td>9</td>
</tr>
</tbody>
</table>

IQR: interquartile range, $\text{SUV}_{\text{max}}$: maximal standard uptake value.
Table 2

Characteristics of the patients with lymph node metastases

<table>
<thead>
<tr>
<th>No</th>
<th>PSA (ng/ml)</th>
<th>Suspicion of ln metastasis in PET/CT</th>
<th>TNM</th>
<th>Gleason score.</th>
<th>Localization of metastatic ln in histopathology</th>
<th>Diameter of metastatic ln in histopathology (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.9</td>
<td>-</td>
<td>pT2c pN1(1/5) pMx G3 R1</td>
<td>7</td>
<td>left obturator node</td>
<td>0.6</td>
</tr>
<tr>
<td>2</td>
<td>38.7</td>
<td>-</td>
<td>pT2c pN1(1/15) pMx G3 R0</td>
<td>7</td>
<td>right obturator node</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>14.2</td>
<td>-</td>
<td>pT3b pN1(1/25) pMx G3 R1</td>
<td>7</td>
<td>right obturator node</td>
<td>n.r.</td>
</tr>
<tr>
<td>4</td>
<td>5.9</td>
<td>left iliac external node</td>
<td>pT3b pN1(1/4) pMx G3 R1</td>
<td>8</td>
<td>left iliac external node</td>
<td>2</td>
</tr>
</tbody>
</table>

ln: lymph node, n.r.: not reported
Table 3

Results from multivariable GEE model for tumor prediction.

Considered prediction variables: tumor configuration, T stage, PSA and Gleason score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Segmental model A</th>
<th></th>
<th></th>
<th></th>
<th>Segmental model B</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>odds-ratio</td>
<td>95% confidence interval</td>
<td>p-value</td>
<td>odds-ratio</td>
<td>95% confidence interval</td>
<td></td>
</tr>
<tr>
<td></td>
<td>min</td>
<td>max</td>
<td>min</td>
<td>max</td>
<td>min</td>
<td>max</td>
<td>min</td>
</tr>
<tr>
<td>Form§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>0.87</td>
<td>1.05</td>
<td>0.56</td>
<td>1.99</td>
<td>0.59</td>
<td>1.17</td>
<td>0.65</td>
</tr>
<tr>
<td>III</td>
<td>0.095</td>
<td>0.5</td>
<td>0.23</td>
<td>1.12</td>
<td>0.168</td>
<td>0.6</td>
<td>0.29</td>
</tr>
<tr>
<td>IV</td>
<td>&lt;0.001</td>
<td>0.18</td>
<td>0.08</td>
<td>0.39</td>
<td>&lt;0.001</td>
<td>0.14</td>
<td>0.05</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 vs. T2</td>
<td>0.39</td>
<td>1.67</td>
<td>0.5</td>
<td>5.3</td>
<td>0.24</td>
<td>1.87</td>
<td>0.65</td>
</tr>
<tr>
<td>PSA in ng/ml</td>
<td>0.68</td>
<td>1.01 #</td>
<td>0.97</td>
<td>1.04</td>
<td>0.26</td>
<td>1.02 #</td>
<td>0.98</td>
</tr>
<tr>
<td>Gleason score</td>
<td>0.19</td>
<td>1.25 $</td>
<td>0.89</td>
<td>1.76</td>
<td>0.18</td>
<td>1.22 $</td>
<td>0.91</td>
</tr>
</tbody>
</table>

§ reference category: Form I
# per a one unit increment of PSA
$ per a one unit increment of Gleason score
Table 4

A. $\text{SUV}_{\text{max}}$ calculated in different intraprostatic entities

<table>
<thead>
<tr>
<th>Entity</th>
<th>N</th>
<th>SUVmax $\pm$ SD</th>
<th>SUVmax (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>454</td>
<td>4.4 $\pm$ 1.5</td>
<td>4.2</td>
</tr>
<tr>
<td>Ca</td>
<td>86</td>
<td>5.7 $\pm$ 3.3</td>
<td>4.9</td>
</tr>
<tr>
<td>BPH</td>
<td>1004</td>
<td>4.6 $\pm$ 1.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>95</td>
<td>4.1 $\pm$ 1.3</td>
<td>3.9</td>
</tr>
<tr>
<td>HGPIN</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

B. Comparison of $\text{SUV}_{\text{max}}$ of different entities

<table>
<thead>
<tr>
<th>Comparison of SUVmax</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCa vs. Normal</td>
<td>0.012</td>
</tr>
<tr>
<td>PCa vs. Prostatitis</td>
<td>0.054</td>
</tr>
<tr>
<td>PCa vs. BPH</td>
<td>0.102</td>
</tr>
<tr>
<td>BPH vs. Normal</td>
<td>0.042</td>
</tr>
<tr>
<td>BPH vs. Prostatitis</td>
<td>p&gt;0.99</td>
</tr>
<tr>
<td>Prostatitis vs. Normal</td>
<td>p&gt;0.99</td>
</tr>
</tbody>
</table>

*Bonferroni corrected

PCa: prostate cancer, BPH: benign prostate hyperplasia, HGPIN: high grade prostate intraepithelial neoplasm
Figure 1
Figure 2
Figure 3a

$SUV_{max}$ vs. PSA (ng/ml)

$r = 0.099, p=0.526$
Figure 3b

Gleason score

SUV_{max}

p = 0.29
The sensitivity of [11C]choline PET/CT to localize prostate cancer depends on the tumor configuration

Michael Souvatzoglou, Gregor Weirich, Sarah Schwarzenboeck, et al.

*Clin Cancer Res* Published OnlineFirst April 14, 2011.

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