Evaluation of the diagnostic accuracy of time-of-flight (TOF) in F-18 choline PET/CT of prostate cancer patients with PSA recurrence: preliminary results of 11 patients

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Purpose

Prostate cancer is the most common malignancy in men (1). Outcome studies among men treated with radical prostatectomy show that relapse rates greater than 30% are common (2). Several studies have shown that Choline PET/CT allows for the detection of even small lymph node metastases as well as local recurrence in patients with increasing prostate specific antigen (PSA) levels post treatment (3). Thus, Choline PET/CT might be beneficiary to guide secondary therapy.

Time-of-flight (TOF) measures the time differences in the line of response (LOR) of a pair of photons originating from positron annihilation which may improve the image signal-to-noise ratio (SNR) (4, 5). Initial investigations of the potential improvements in SNR by TOF were published in 1980 (6). Recent studies have shown that using TOF PET, improved image signal-to-noise ratio that is proportional to the square root of the object size and inversely proportional to the square root of the system timing resolution could be obtained (7). These results correlate with patient studies in which lesions are seen more clearly and with higher uptake at comparable noise with TOF than without TOF (8).

TOF advantages may include better definition of small lesions and image details, improved uniformity, and noise reduction (3). Recent work with TOF PET has demonstrated improvement in image characteristics such as spatial resolution, contrast, and voxelwise noise (4, 8, 9).

While specific estimates can be made for phantom imaging, the beneficial effects of TOF PET is more difficult to quantify in clinical applications (3). TOF may improve lesion detection and localization for clinically challenging tasks. In particular, TOF benefit image quality in obese patients (10), which is of importance in critical regions like the abdomen and pelvis, where most of the metastatic lymph nodes of prostate cancer patients are located. It was demonstrated that the detection rate of recurrent disease using Choline-PET/CT could be related to the serum PSA-level. Low PSA-levels were associated with lower detection rates. (11).

The purpose of this study was to evaluate the impact of a TOF on the lesion detection rate on a PSA-level dependent basis and to evaluate image quality and quality of lesion demarcation using a modern 3-D high-definition PET/CT scanner in comparison to a standard PET/CT reconstruction algorithm. Secondary object was to evaluate the impact of TOF on the objective parameters lesion size and SUV_{max}. 
Patients

Thirty-two prostate cancer patients (mean PSA 8.87 ng/ml ± 17; mean age: 71 years ± 7.8) with biochemical recurrence who were referred for a whole-body 18F-Choline PET/CT examination for cancer re-staging were included in this study. Biochemical recurrence was defined as an increase of PSA to values of more than 0.4 ng/ml (12). The local ethics committee approved the study.

18F-Choline PET/CT Protocol

The imaging protocol was described in a similar manner as part of a recent study from the same institution (13). All patients maintained a standardized uptake phase of 60 minutes that allowed tracer (mean 345 ± 24 MBq) to accumulate in relevant lesions. Patients were imaged on the Biograph mCT (Siemens Healthcare Sector, Erlangen, Germany) with a 5.0-mm spatial resolution in 3-D mode. The system consists of 3 detector rings with an axial coverage of 16 cm. For whole-body PET/CT from the skull to the mid thighs, 8 different bed positions were necessary in most cases.

First, a low-dose helical CT scan to correct attenuation was acquired during shallow breathing (using CARE Dose4D [Siemens]: 50 mA, 120 kVp, pitch of 0.8, and collimation of 1.2 mm) with the arms elevated over the head. Immediately thereafter, PET was performed beginning from the mid thigh. Patients in whom diagnostic imaging had not been recently performed were subsequently examined using contrast-enhanced (CE) diagnostic CT with body weight-adapted iodinated intravenous contrast medium (Imeron 320; Bracco, Ort vom Hersteller). In patients who had recently undergone diagnostic CT, no further CE-CT was performed; however, the radiation dose of the attenuation-corrected CT was increased in the latter to the CARE Dose4D-adapted 80 mA to achieve adequate image quality for improved correlation of the morphologic results derived by CT with the PET images. Dead time of the PET system as well as random and scatter events were corrected as well. Images were subsequently calculated using TOF. Patients had no additional radiation exposure.

Images were interpreted at a workstation equipped with fusion software that can display CT, PET, and PET/CT images (MMWP, VE31A; Siemens Healthcare Sector, Erlangen, Germany). All PET/CT images were read by two board-certified nuclear medicine specialists and a third-year nuclear medicine resident in consensus in a blinded manner. The primary tumor, a maximum of 5 lymph node metastases, and a maximum of 2 lesions per organ (maximum of 5 lesions), adapted to the Response Evaluation Criteria in Solid Tumors, 1.1, were assessed (14).
Image quality was scored on a 5-point Likert-type scale as follows: 1, excellent; 2, good; 3, moderate; 4, poor; and 5, very poor image quality. Lesions were visually identified. The quality scoring was predominantly based on individual subjective image perception. Objective criteria were image blurring (background uptake) and, in terms of the quality of lesion demarcation, the relation of lesion uptake to background uptake. Other criteria were the sharpness of angles of anatomic structures other than the lesions for determination of overall image quality.

For the quantitative outcome, tumor uptake was measured using $\text{SUV}_{\text{max}}$, and lesion volumes were determined. Volumes of interest were placed around the lesions to estimate volume with an SUV threshold of 2.5. $\text{SUV}_{\text{max}}$ was computed after tissue radioactivity had been normalized to the decay-corrected injected dose and body weight. Gold standard was reevaluation of the lesions by means of CT or PET/CT from 02/2012 until 12/2012 as part of the clinical follow-up.

Statistics

Wilcoxon tests were obtained to evaluate overall image quality and the quality of lesion demarcation in TOF and standard images. Pearson’s correlation coefficients were measured and t-tests performed to compare the lesion volumes and $\text{SUV}_{\text{max}}$. Statistical evaluation of the image quality and lesion detection rate was based solely on the results of the board-certified nuclear medicine specialists. Kappa-values were obtained additionally for image quality and quality of lesion demarcation to compare interobserver agreement between board-certified nuclear medicine physician and third-year resident.
Results

Patients and Lesions

All 32 patients with biochemical recurrence of prostate cancer (PSA >0.04 ng/ml) were included in this study. Twenty-one patients had a PSA level of #5ng/ml, whereas 11 patients had PSA-levels of # 5mg/l. Overall, a total of 76 lesions were assessed. Lesions were local recurrence (n=7), lymph nodes (n =41), bone lesions (n=27) and one pulmonary lesion.

Image Quality and Lesion Detection Rate

Image quality was reduced in calculated TOF-images. (standard: 1.28; TOF: 1.77; p<0.01) (Table 1 a; Fig. 1 a and b). Nevertheless, the image quality was rated as excellent or good in 97% of those scans. On the other hand, the quality of lesion demarcation was improved (standard: 1.66; TOF: 1.26; p<0.01) (Table 1 b; Fig. 1 a and b). Eight additional lesions were detected using TOF (SUV\textsubscript{max}3.64 ± 0.95; lesion volume 0.58 ± 0.5 cm\textsuperscript{3}) (Table 1 c; Fig. 1 a and b). In 19% (n=4) of the patients with a PSA level # 5mg/ml additional lesions could be detected. None of the examination showed additional metastases on TOF reconstructions, if no metastases were apparent on standard PET images.

Lesion Volume

The mean lesion volume was 5.3 cm\textsuperscript{3} (± 10.4 cm\textsuperscript{3}; range, 0.05-54 cm\textsuperscript{3}) on standard images and 5.4 cm\textsuperscript{3} (± 10.3 cm\textsuperscript{3}; range, 0.05 - 53.2 cm\textsuperscript{3}) on TOF-calculated images (Fig. 2). Pearson showed excellent correlation between standard and TOF images (p>0.01). The t-test did not indicate a significant difference between image volumes of both groups (p= 0.41).

SUV\textsubscript{max}

SUV\textsubscript{max} was significantly increased in TOF-calculated images (without TOF: 6.9 ± 4.1; range, 2.0 - 21.0; TOF: 8.1 ± 4.1; range, 2.6-21.0; p< 0.01) (Fig. 3). Nevertheless, Pearson correlation coefficient showed excellent correlation between standard and TOF images (p<0.01). The mean SUV\textsubscript{max} was 6.9 (SD, 4.1; range, 2.0 - 21.0) on standard images and 8.1 (SD, 4.1; range, 2.6-21.0) on TOF images (Figure 3).

Interobserver agreement
Comparing the results of the two board-certified nuclear medicine physicians and the first-year resident showed limited interrater agreement on the overall image quality ($K_{\text{standard}}=0.29$; $K_{\text{TOF}}=0.17$), as well as on the quality of lesion demarcation ($K_{\text{standard}}=0.55$; $K_{\text{TOF}}=0.21$). Subsummation of ratings 1=excellent and 2=good and ratings of 3=moderate and 4=poor and comparison of these combined values between both observers led to an increase of interrater agreement to values of $K=1.0$ on standard examination and $K=0.65$ on TOF for overall image quality and values of $K=0.74$ on standard examination and $K=0.66$ on TOF for quality of lesion demarcation (Table 2). None of the relevant lesions were missed by the third-year resident on both, the standard and TOF images.
Fig. 1: The upper 18F-Choline-PET image shows standard image, whereas below the same slice after application of TOF reconstruction algorithm is demonstrated. TOF clearly shows pathological uptake of a pararectal lymph node that is also visible on the CT image. Additionally, suspicious uptake of the right angle of sacrum is shown which is not apparent on standard PET image (red arrows).

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Fig. 2: The upper 18F-Choline-PET image shows standard image, whereas below the same slice after TOF-reconstruction is demonstrated. TOF clearly shows pathological uptake of an additional paraaortic lymph node that shows no pathological uptake on standard images. Two more lymph nodes with slight uptake are visible on the same slice solely on TOF images (red arrows).

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Fig. 3: Comparison of lesion size of standard (blue) and TOF images is presented in units of cm³ (logarithmic). Trendlines as well as values do not indicate a significant difference between TOF and standard PET images.

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Fig. 4: Comparison of SUVmax of standard (blue) and TOF is presented. Trendlines as well as values indicate a significant difference between TOF and standard PET images.

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Table 1: Comparison of overall image quality of Choline-PET/CT images in all 32 prostate cancer patients between TOF and standard reconstruction algorithm. Image quality was scored on a 5-point scale as follows: excellent quality = 1, good quality = 2, moderate quality = 3, poor quality = 4 and very poor image quality = 5.

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Table 2: Comparison of lesion demarcation of Choline-PET/CT images in all 32 prostate cancer patients between TOF and standard reconstruction algorithm. Lesion demarcation was scored on a 5-point scale as follows: excellent quality = 1, good quality = 2, moderate quality = 3, poor quality = 4 and very poor image quality = 5.

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Table 3: Comparison of results of board-certified nuclear medicine physician and third-year resident showed limited interrater agreement for ratings on overall image quality and quality of lesion demarcation. Subsummarization of ratings 1=excellent and 2=good and ratings of 3=moderate and 4=poor and comparison of these combined values between both observers led to an increase of interrater agreement.

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Table 4: Comparison of demarcation of additional lesions of Choline-PET/CT images in all 32 prostate cancer patients in TOF images. Quality of lesion demarcation was scored on a 5-point scale as follows: excellent quality = 1, good quality = 2, moderate quality = 3, poor quality = 4 and very poor image quality = 5.

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Conclusion

Application of TOF in prostate cancer patients with elevated PSA levels after first line treatment seems to be of additional value to detect small metastatic lesions using modern 3-D HD PET/CT scanner, which may have further clinical implications on image-guided radiation therapy. Previous studies on lesion detectability by TOF using different observers described improved lesion detectability in uniform objects with improving temporal resolution. Detectability for 10 mm diameter hot spheres estimated using a non-pre-whitening matched filter (NPW SNR) improves nonlinearly with TOF. The gain in image quality using contrast-to-noise measures was proportional to the object diameter and inversely proportional to the temporal resolution of the scanner (15). The existing data indicate that TOF information leads to increased lesion detectability, which is achieved with less iterations of the reconstruction algorithm. Results in phantom studies indicate that TOF PET will allow to shorten scan times and improve lesion detectability, especially in large patients, which is of great value in potential further clinical applications (16). With statistical noise present in PET images, detecting a lesion at an unknown position is more challenging and thus may represent a more clinically relevant task (10). Moreover, lesion size may be of particular interest if PET images are used in radiation oncology treatment planning (17). Accurate delineation of target volumes is important to maximize radiation dose to the tumor and minimize it to non-tumorous tissue (18). Our data demonstrate that the PET/CT volumes measured are not significantly influenced by the application of the TOF reconstruction algorithm.

Using image guidance to map the radiation field allows for a more selective application of higher doses in smaller target areas which will in consequence diminish the deteriorating side effects of radiation therapy in the adjacent non-tumorous tissue. (19). Moreover, more aggressive treatment techniques allowing dose escalation to positive paraaortic lymph nodes could be facilitated by means of PET/CT-guided intensity-modulated radiation therapy (IMRT). Target coverage and normal tissue sparing that should facilitate the more aggressive treatment can be optimized by the use of PET/CT for treatment planning (20). TOF may help to further reduce treatment margins if single metastatic lymph nodes could be identified and sufficiently distinguished from benign lymph nodes in order to protect abdominal organs from unnecessary radiation exposure.

TOF could also be useful to lower tracer dose in patients with multiple PET studies in order to reduce radiation exposure. A study by Murray et al. investigated to what extent a reduction in administered activity, synonymous with an overall reduction in repeated patient exposure, compromised the accuracy of quantitative measures using time-of-flight PET/CT. The study demonstrated that short time acquisitions, synonymous with reduced injected activity, performed on a TOF-based PET/CT system are feasible without encountering significant bias which could translate into clinical protocols using lower administered activities (21).
Subjective image perception was only slightly adversely affected by application of TOF-image reconstruction algorithm. Nevertheless, this finding is not in line with the results of other research groups that indicated noise reduction by application of TOF (3). On the other hand, image quality was rated as excellent or good in 97% of the scans (Fig.1, Table 2).

We found a significant difference between the SUV\textsubscript{max} values of lesions with an increase in SUV\textsubscript{max} related to TOF (Table 3). This is important as uptake is semiquantitatively used in order to distinguish between benign and malignant lesions and changes in SUVs serve to monitor response to therapy (13). These findings indicate a limited value of PET to monitor therapy if comparative examinations were carried out with and without application of TOF. In respect of this possible pitfall, SUV\textsubscript{max} - thresholds may have to be adapted if TOF is used.

Finally, previous experiences have demonstrated that TOF helps unexperienced observers to detect focal warm lesions. A recent study used numeric and nonclinician human observers to measure the impact on lesion detection and localization. TOF-PET provided a significant improvement in observer performance for detecting focal warm lesions in a noisy background (4). In our study, interobserver agreement was reasonable on overall image quality and quality of lesion demarcation between board-certified nuclear medicine physician and first-year resident. None of the relevant lesions were missed by the first-year resident on both standard and TOF images. A suspected increase of lesion detection rate in unexperienced observers using TOF could not be confirmed by our results. Moreover, a difference between lesion detection rate and the PSA-level that was indicated by a recently published study by Krause et al. was not apparent in our study (11).

Our study had some limitations. First, we did not obtain histopathologic proof of our findings because most patients with recurrent cancer had multiple lesions and received either systemic or radiation therapy treatment. In none of the patients lymphadenectomy based on the results of PET examination was performed. Other than that, in only half of the patients a follow-up examination (CT= 14; PET/CT= 2) was performed to confirm initial findings. Moreover, the group size of 32 patients is still relatively small.

Future studies will be needed to assess the true clinical value of application of TOF in larger cohorts of prostate cancer patients with PSA recurrence.

In prostate cancer patients with biochemical recurrence application of TOF-software in \textsuperscript{18}F-Choline-PET/CT seems to be of additional value to detect small metastatic lesions, which may have an impact on PET-guided radiation therapy, particularly in critical regions such as the abdomen and pelvis, even though use of TOF-software may result in a substantial decrease of specificity if no adaption of SUV\textsubscript{max} - thresholds is applied.
References


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