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REVIEW ARTICLE

Focus on time-of-flight PET: the benefits of improved time resolution

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Abstract TOF PET is characterized by a better trade-off between contrast and noise in the image. This property is enhanced in more challenging operating conditions, allowing for example shorter examinations or low counts, successful scanning of larger patients, low uptake, visualization of smaller lesions, and incomplete data sampling. In this paper, the correlation between the time resolution of a TOF PET scanner and the improvement in signal-to-noise in the image is introduced and discussed. A set of performance advantages is presented which include better image quality, shorter scan times, lower dose, higher spatial resolution, lower sensitivity to inconsistent data, and the opportunity for new architectures with missing angles. The recent scientific literature that reports the first experimental evidence of such advantages in oncology clinical data is reviewed. Finally, the directions for possible improvement of the time resolution of the present generation of TOF PET scanners are discussed.

Keywords TOF PET · Time-of-flight · Dose · Image quality · Signal-to-noise · Time resolution · Detectability

Introduction

Time-of-flight (TOF) positron emission tomography (PET) is becoming the new standard technology for all major PET scanner manufacturers thanks to the discovery of new fast scintillators, improvements in the electronics, the availability of cheaper computing power, and the advance in reconstruction methods [1–4]. The first attempt at TOF PET dates back to the 1980s, at which time reconstruction methods and PET scanner prototypes were being developed [5–9]. The first TOF PET scanners were based on CsF and BaF_2, scintillators characterized by very short decay times, but also by severe limits including low density, low photoelectric fraction, and low light yield. Bismuth germanate ($Bi_4Ge_3O_{13}$, BGO) became increasingly used due to its high density and therefore high detection efficiency, but its slow decay time makes it inadequate for TOF PET, and the research into TOF PET was brought to a temporary halt. In fact, the time resolution, or the accuracy in resolving the time difference between the arrivals of coincidence photons at two detectors, is a key parameter for a TOF PET scanner, but cannot fully compensate for poor detection efficiency or low spatial resolution. Because of this, BGO-based scanners outperformed the first generation of TOF PET scanners.

The present generation of TOF PET scanners use new scintillators that are in general fast to allow good time resolution, and also have some attractive characteristics lacking in the scintillating materials of the 1980s including high density and atomic number (high detection efficiency), good energy resolution (good scatter rejection), and high light yield (good position identification and time resolution). The most common scintillators with these characteristics are lutetium orthosilicate (Lu_2SiO_5, LSO), its derivate LYSO ($Lu_{2-x}Y_xSiO_5$), and lanthanum bromide ($LaBr_3$). LSO and LYSO are fast scintillators, with good light output, high density, and large mean atomic number Z_{eff}. $LaBr_3$ is faster and brighter, but its lower density and Z_{eff} result in lower sensitivity and poorer spatial resolution. The advantages of TOF PET are closely related to the system time resolution, which ranges from 500 to 600 ps in the

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present generation of commercial TOF PET scanners based on LSO and LYSO [10–12]. Research TOF PET scanners using $LaBr_3$ can reach 375 ps [13].

Even though the deployment of this new generation of TOF PET scanners is still limited, there is already clear evidence of the advantages of TOF over conventional (or non-TOF) reconstruction in the clinical environment. We review here the experimental evidence for these benefits that relate to the time resolution of a TOF PET scanner, present some clinical evidence for these benefits from the recent scientific literature, and discuss future avenues towards improved time resolution.

Signal-to-noise in TOF PET

A key characteristic of TOF PET is the improvement in image quality due to increased signal-to-noise ratio (SNR). This is directly tied to the mechanism of radiation detection in the PET scanner. When two back-to-back photons are emitted by the annihilation of a positron in the tissue, for example emitted by a ^{18}F-FDG decay, the photons reach two opposite detectors of a PET scanner at different times. The TOF difference is proportional to the path length difference of the two photons, and this provides information on the position of the annihilation along the straight line joining the detectors. In fact, the position is blurred by a time measurement uncertainty named "time resolution", which depends on several instrumental factors. The smaller the time resolution Δt, the smaller the error on the localization of the source Δx. Space and time uncertainty are proportional according to Eq. 1, where c is the speed of light:

$$Dx = cDt/2 \tag{1}$$

If accurate time measurement could be achieved, no tomographic reconstruction algorithm would be necessary, since the position of the source along the line could be assessed accurately to provide corresponding high spatial resolution. In order to achieve a 2-mm single pixel spatial resolution, a 10-ps time resolution would be required. In today's TOF PET scanners, such time measurement accuracy is not achievable, but the TOF information is incorporated in the tomographic reconstruction algorithm, and contributes to the process of estimating the radioactivity distribution that best generates the measured projection data. In fact, tomographic reconstruction is known to be mathematically ill-conditioned. This means that small errors in the input data will cause large errors in the final image. With the additional TOF information, the problem becomes less ill-conditioned, and this is at the root of the advantageous properties of TOF reconstruction, such as reduced noise amplification during reconstruction and lower sensitivity to errors in the data corrections used, which we discuss later in this paper.

During the process of back-projecting the coincidence data from the projection space into the image space, a probability function is used along the line-of-response between the two detectors that are hit. This probability function, or TOF kernel, which is typically a bell-shaped curve resembling a gaussian distribution, is centred on the position corresponding to the measured TOF and has a width corresponding to the time resolution of the scanner. The TOF weighting process reduces propagation of the statistical noise in the image. In each spatial position, only coincidence events with TOF differences consistent with such positions are accumulated. Moreover, the random coincidences counted at each detector pair are distributed according to their TOF information along the line-of-response, and do not affect all voxels crossed by the line [14]. The overall effect is lower noise and higher contrast recovery; in other words, higher SNR.

In particular, the SNR in a TOF image improves with decreasing time resolution Δt (or the corresponding spatial uncertainty Δx) and it is larger for larger patients (being related to the effective diameter D). The TOF SNR is proportional to the non-TOF SNR, through the following relationship [1, 2, 4, 14–20]:

$$SNR_{TOF} = \sqrt{\frac{D}{\Delta x}} \cdot SNR_{non-TOF} \tag{2}$$

The ratio between SNR_{TOF} and SNR_{nonTOF} is commonly referred to as TOF SNR gain. It has been shown that SNR is in turn proportional to the square root of the noise effective counts (NEC) in a PET scan, or $SNR \propto \sqrt{NEC}$ [21]. Thus, a gain in SNR can be seen as a gain in counts: a TOF image is equivalent to a non-TOF image obtained with a larger number of counts or, in other terms, TOF reconstruction acts as a "virtual counts or sensitivity amplifier" for a PET scanner.

Equation 2 holds only for large objects. If the tomographic dimensions of the patient D are close to the spatial uncertainty Δx associated with the time resolution, the SNR gain approaches 1 and TOF would not be expected to produce any SNR gain. The present generation of commercial TOF PET scanners has a time resolution between 500 and 600 ps. Preliminary attempts to perform TOF reconstruction on non-TOF PET scanners showed that a SNR gain was measurable even with time resolution of only 1.2 ns [22]. In Table 1, the estimated TOF SNR and NEC gain are presented as a function of the time resolution, given a patient effective diameter of 40 cm. The limit of a time resolution equivalent to the patient size is added as a non-TOF reference.

Table 1 Time resolution, spatial uncertainty and estimated TOF gain for a 40-cm effective diameter patient

Time resolution (ns)	Δx (cm)	TOF NEC gain	TOF SNR gain
0.1	1.5	26.7	5.2
0.3	4.5	8.9	3.0
0.6	9.0	4.4	2.1
1.2	18.0	2.2	1.5
2.7	40.0	1.0	1.0

Equation 2 can be considered a reasonable estimate rather than an accurate calculation of the TOF gain, since it is derived using several hypotheses and approximations: it represents the estimate of the SNR gain measured at the centre of a cylinder, uniform in density and activity distribution, located in the centre of the field of view; it assumes perfect attenuation, scatter, and random correction; and the analytical reconstruction used is such that the noise propagation from projection space to image space is linear. In a clinical case, the radioactive tracer distribution is not uniform, nor is the density in the patient. Also, an iterative reconstruction is commonly used. Since iterative algorithms are not linear, the noise in the image is also not linear with the noise in the measured projection data.

Iterative reconstruction methods, for example maximum likelihood expectation maximization (MLEM) and the faster ordered subset expectation maximization (OSEM) or row action maximum likelihood algorithm (RAMLA), are typically preferred in clinical practice over analytical methods such as filtered back-projection, because of the lower noise level and the better noise structure. However, they introduce an additional variable, the iteration number. In MLEM, OSEM and similar iterative algorithms, the contrast recovery improves with the iteration number, but the image noise also tends to increase with the iteration number (unless some relaxation parameter or regularization is used). The noise–contrast balance is commonly set by an arbitrary choice of when to stop the iteration process. Constraints of clinical reconstruction time also influence the choice. If iterative algorithms are used, the additional TOF information aids the reconstruction to converge more quickly to the "true" image, usually with a simultaneous increase in contrast and noise. The balance between contrast recovery and noise is different between non-TOF and TOF methods, mainly because of the faster convergence of TOF.

In theory, when the same final convergence value is reached by both methods, the SNR in the TOF image should be higher than the SNR in the non-TOF image by a factor close to that estimated by Eq. 2. In clinical practice, the iterative process is interrupted before full convergence. In order to compare TOF and non-TOF reconstructions, one must decide at what level of the iteration process such comparison needs to be done. Several approaches can be and have been used by different researchers: comparing images at the iteration that optimizes the SNR, which is not always the same for TOF and non-TOF; comparing images that have reached some given contrast recovery value, usually not the same iteration for TOF and non-TOF; comparing images at a given noise level, usually not the same iteration for TOF and non-TOF; comparing images at the same iteration. The first two choices typically exploit the noise reduction capability of TOF, and the second two exploit the faster convergence and higher contrast recovery. In any case, improved SNR should be observed in TOF images, as is shown in the following sections.

How to exploit the advantages of TOF PET

There are different ways to use the improved SNR associated with TOF PET. There are also additional advantages associated with TOF reconstruction that derive from the time and spatial information carried by TOF data. First, the SNR gain can be seen as a counts multiplier or a sensitivity amplifier. The virtual increased sensitivity of TOF PET can be directly exploited in three ways. For a given acquisition time and dose to the patient, (1) TOF can provide better image quality and improved lesion detection, (2) the scan time can be shortened while keeping the same image quality with better clinical workflow and added comfort for the patient, and (3) the dose to the patient can be reduced with the same scan time and image quality.

In this section we review these and other advantages and point to some directions that can be followed to exploit them.

Patient size equalizer

In oncology practice, typically a longer acquisition time is needed for a larger patient characterized by higher attenuation. Often the longer acquisition time does not compensate for the poor quality of the data. A first immediate positive characteristic of TOF PET, which stems from Eq. 2, is that the TOF SNR gain is larger for larger patients. Because of the higher attenuation, larger patients are affected by more noise. TOF acts as an equalizer, bringing the image quality in larger patients closer to that in patients of average size.

Image quality improvement

In Fig. 1, two coronal images reconstructed from a non-TOF scan and a TOF scan in a patient with lung cancer are presented. The data were acquired on a Siemens mCT TOF

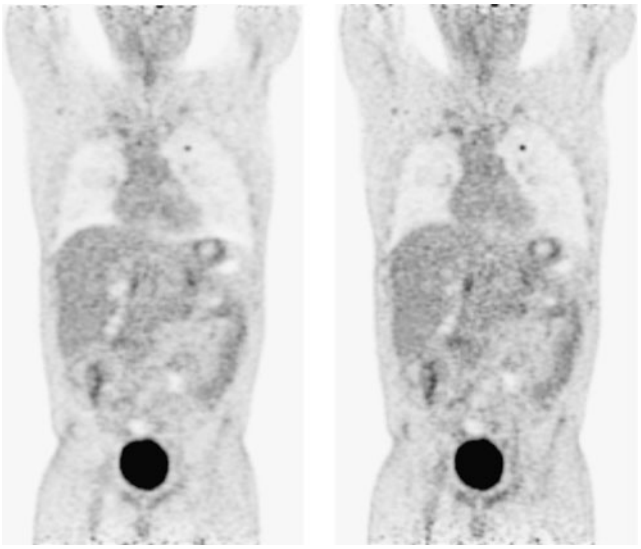

Fig. 1 Coronal images reconstructed from a non-TOF scan (*left*) and a TOF scan (*right*) in a patient with lung cancer. The acquisition time was 3 min per bed position for both images. At the same number of counts, the image quality is better with the TOF reconstruction

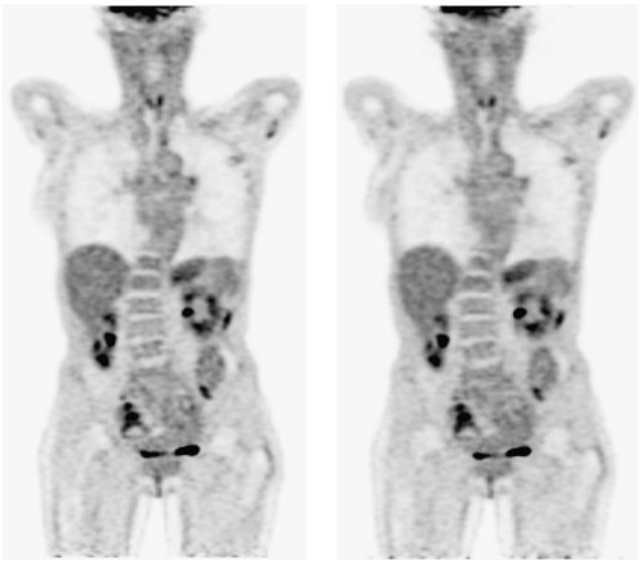

Fig. 2 Coronal images reconstructed from a non-TOF scan (*left*) and a TOF scan (*right*). The acquisition time was 2 min per bed position for the non-TOF scan and 1 min per bed position for the TOF scan. The quality of the non-TOF image and that of the TOF image with half of the counts are similar

PET/CT scanner [10]. The images were reconstructed using 3D OSEM incorporating point spread function (PSF) into transaxial images with a 4-mm pixel size and 2-mm axial plane separation. The scan was based on an acquisition time of 3 min per bed position, and all counts were used for both reconstructions. In both reconstructions, 21 subsets and three iterations were used, and no post-reconstruction filter was applied. The TOF image quality is better in terms of noise, contrast recovery, and resolution of uptake details. For example, the uptake focus in the left lung is sharper, and the uptake in the rib cages is more clearly defined.

Examination time reduction

In Fig. 2 images from the same scanner with the same reconstruction methods in another patient are shown. In this patient, the scan was based on an acquisition time of 2 min per bed position, but only 60 s of data were used for the TOF reconstruction. Reconstruction parameters were 21 subsets and three iterations in non-TOF reconstruction and 14 subsets and two iterations in TOF reconstruction with no post-reconstruction filter was applied on either. The comparison shows that the TOF image is very similar in terms of noise and contrast to the non-TOF image with twice the counts.

Dose reduction

A third option opened by TOF PET counts amplification is the possibility of dose reduction. Presently, there is great interest in reducing the dose of a PET/CT study: both low-dose CT and low-dose PET are being explored. In particular, reducing the dose of a PET examination will reduce not only the cancer risk by radiation exposure of the patients [23], but also the occupational radiation exposure of professionals in the clinical environment [24]. A low-dose TOF PET scan can produce image quality similar to that of a standard dose conventional PET scan with the same scan time. Some clinical studies have already explored this possibility and are discussed in this article below [25].

Higher spatial resolution

Another opportunity made available by TOF is a reduction in pixel size in clinical oncology images. The spatial resolution of standard PET scanners is typically not exploited in oncology. In order to improve comfort and patient work-flow, a typical whole-body oncology scan today is only 1–3 min per bed position. Because of the low statistics, an image pixel size larger than the limit of the PET scanner is preferred in order to have higher counts per pixel and obtain a lower noise image. For example, typically an image pixel size around 4 mm is used in oncology even when a higher resolution option (2-mm pixel size) is available. Using a larger pixel size is equivalent to applying a low-pass filter on the image, blurring the image and therefore degrading the spatial resolution.

The lower noise and amplified effective sensitivity of TOF reconstruction allow the exploitation of the resolution limit of the PET scanner, possibly improving the detection of small lesions. In Fig. 3, patient images obtained on a

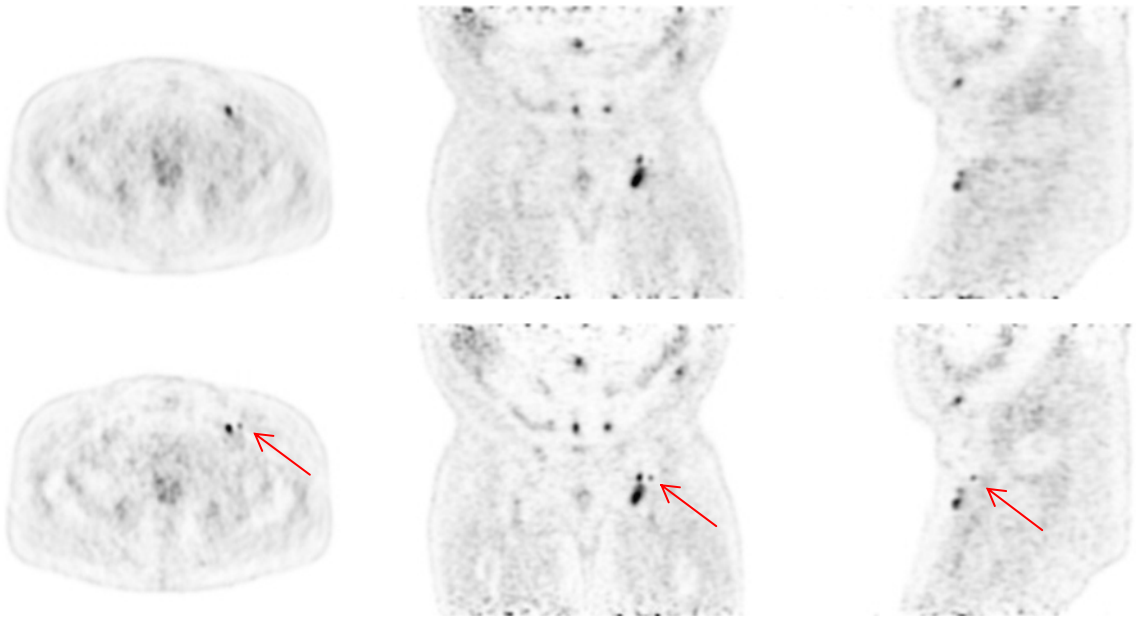

Fig. 3 Transaxial, coronal and sagittal images in a patient with nodules in the pelvic region showing FDG uptake (*top* non-TOF image, *bottom* TOF image). *Arrows* uptake focus not visible in the non-TOF images

Siemens mCT TOF PET scanner are shown. In this case, the images were reconstructed with 3D OSEM with PSF, using the maximum resolution with a 2-mm isotropic voxel size, and both the TOF and non-TOF reconstructions used 14 subsets and two iterations, with a 5-mm post-reconstruction filter. In the TOF images, one additional small uptake focus, not visible with the conventional non-TOF reconstruction, was clearly visible.

Imaging or dosimetry with extremely low statistics

While most of the oncology PET examinations today are performed using ^{18}F-FDG and a standard injection typically around 300 MBq, there are more challenging tracers and scanning conditions that are or could be used in PET. TOF PET can provide the tools to push the limits of what can be imaged today with a PET scanner. For example, the use of TOF PET for monitoring the dose in cancer internal radiotherapy was proposed in a recent study. This study showed that it is possible to perform dosimetry assessment in internal radiotherapy with ^{90}Y, which has a very low branching ratio of internal e^+ e^- pair production, but is still detectable and quantifiable with TOF PET [26].

Overcoming inconsistent or missing data

A new set of improved performances stems from the time and spatial information carried by TOF data that can be used to overcome missing or inconsistent data. The TOF information on the position of the source along a line of response can compensate for information that is missing because of incomplete angular coverage of the patient due to special PET scanner architectures. For example, a dedicated breast TOF PET scanner [27] and an in-beam TOF PET system for hadron-therapy treatment facilities have been proposed [28].

The other interesting characteristic of TOF reconstruction is that it is a more robust reconstruction method in the presence of correction data that is inconsistent with the emission data. In order to obtain quantitative PET images, the original emission data need to be corrected for contamination from random and scatter coincidences, for attenuation in the tissue, and for the individual detector's response (normalization). These corrections are estimated with theoretical models or simulation, or are measured, but such estimates are never error-free. If the corrections are not accurate or consistent enough with the measured emission data, artefacts appear in the image. There is evidence that TOF reconstruction is less sensitive to erroneous normalization and poorly estimated scatter correction [4, 29, 30], as well as to mismatched attenuation correction [4, 31]. The TOF information tends to compensate for the inaccurate attenuation information and redistribute the annihilation events accordingly.

A simple experiment performed on a Siemens mCT TOF PET scanner with a NEMA 2001 image quality phantom [32] to demonstrate this robustness to flawed attenuation correction has been reported. The phantom had uniform ^{18}F background in water, four spheres filled with water containing ^{18}F at a concentration of 4:1 to the background, two larger spheres filled with water but no activity, and a 5-cm diameter central cylindrical cavity with air and very low

density polystyrene. Two attenuation correction arrays were used. The first was computed from the CT using a segmentation that assigned either the attenuation value of water at 511 keV (0.096 cm^2/g) or that of vacuum (0.0 cm^2/g) to all voxels. The second was obtained from the first, but the attenuation of water was also assigned to the internal cavity. TOF and non-TOF images were reconstructed using the very inaccurate second attenuation map. The comparison can be seen in Fig. 4; as a reference, the TOF image obtained with CT-based accurate attenuation correction is also shown.

In the non-TOF image (Fig. 4d), the region within the internal empty cylinder is clearly overcorrected for attenuation, resulting in an apparent high activity concentration, even higher than that of the background. In the TOF image (Fig. 4e) this artefact is greatly reduced. The activity in the cavity is lower than that of the background and closer to the zero activity level visible in the unbiased TOF image Fig. 4f).

The characteristic of being less sensitive to inaccurate corrections typical of TOF can be very useful not only to reduce accidental artefacts in the system due to detector working conditions drifting over time, CT artefacts and motion correction artefacts, but also to allow for the TOF PET system to work with low cost, low quality CT or in situations where an accurate attenuation map is not available, as in PET/MRI.

Clinical evidence of the benefits of TOF PET

In recent years, experimental evidence of the benefits of TOF reconstruction has been demonstrated in patient studies, particularly in oncology. All recently published studies performed on different PET scanners and using different iterative reconstruction methods have shown common findings. TOF reconstruction offers better contrast recovery at the same noise level (or lower noise at the same recovery level), better detection of small lesions, and faster convergence with iterative algorithms.

The first study by Karp et al. [33] performed on a Philips Gemini TF PET/CT scanner included images from five oncology patients reconstructed by both non-TOF and TOF methods. The study showed a clear visual improvement in image quality due to TOF. Moreover, a detailed investigation of uptake values in small lesions (1–2 cm) showed that TOF reconstruction converged more quickly (higher measured uptake at the same number of iterations). In fact, TOF images seemed to converge to a higher uptake value, at least as long as the number of iterations was kept within a (clinically) realistic number (less than ten). As shown in Fig. 5 [33], for all seven lesions selected in this patient image, the curves that describe the uptake values in the lesions as a function of the iteration number (or the corresponding noise measured in the liver) were higher if TOF reconstruction was used. A phantom study reported in the same article showed that the improvement was even higher if the phantom or patient size were larger. A correlation between the amplitude of the TOF contrast gain and patient body mass was also observed.

Kadrmas at al. [34] used a prototype Siemens TOF PET/CT scanner (equivalent to the commercial Siemens mCT scanner) and an anthropomorphic phantom to perform a controlled detectability study under pseudoclinical conditions. ^{68}Ge warm spherical lesions (26 lesions, diameter 6–16 mm) were placed in various locations in the phantom

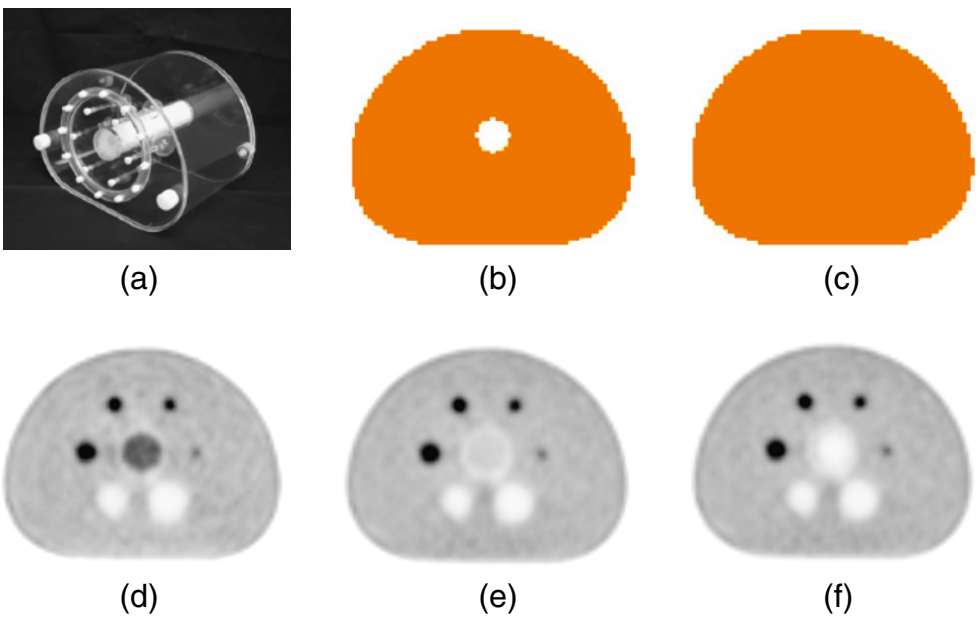

Fig. 4 The image quality phantom (**a**), the correct attenuation map (**b**), the incorrect attenuation map (**c**), the non-TOF image obtained using the incorrect attenuation (**d**), the TOF image obtained using the incorrect attenuation (**e**), and the TOF image obtained using the correct attenuation (**f**) as a reference

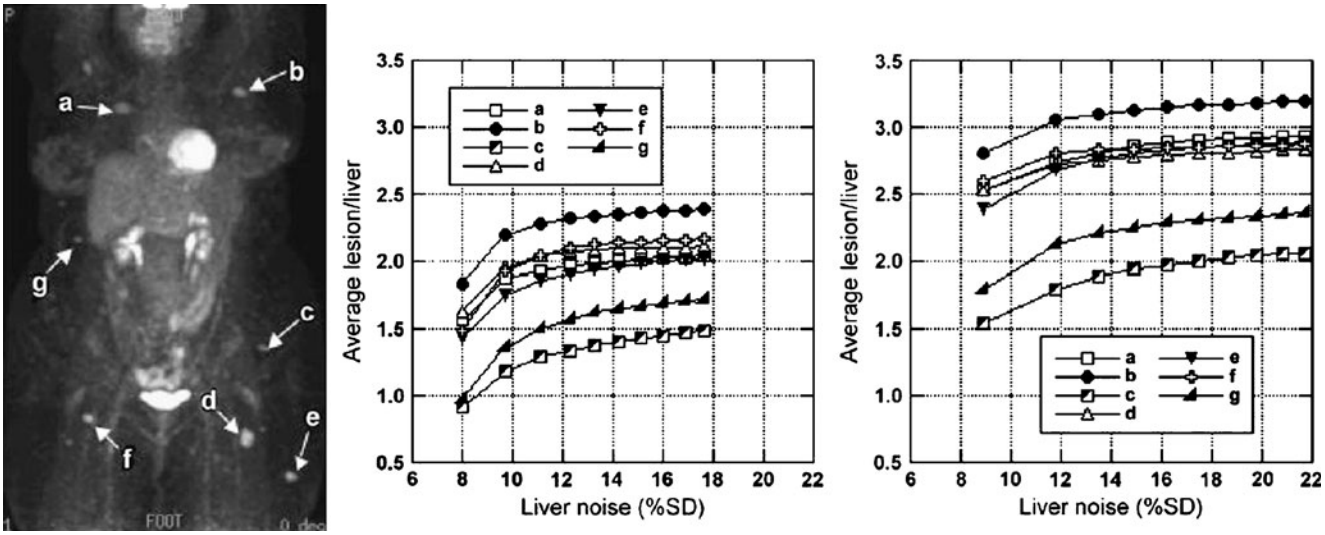

Fig. 5 Patient with non-Hodgkin's lymphoma. *Left*: Anterior projection image (*a–g* selected lesions). Uptake values in the lesions normalized by the average uptake in the liver are plotted vs. noise for non-TOF (*centre*) and TOF (*right*) reconstructions; each point represents an iteration (from reference [33])

filled with background ^{18}F solution. PET scans were performed using background activity and scan protocols similar to a clinical situation. After TOF and non-TOF reconstruction, detectability was evaluated using both numerical and human observers. Since the intensity and the location of the lesions in this controlled experiment were known, quantitative comparison of the detectability was possible. Different metrics were used to quantify the detectability. In particular, the area under the LROC curve for numerical observers was 0.516±0.051 for the non-TOF scans and 0.813±0.046 for the TOF scans. For the human observers, equivalent values were 0.662±0.087 and 0.873±0.062. Both cases showed clear evidence of higher detectability for TOF reconstruction beyond experimental error.

Lois et al. [35], using the same prototype Siemens TOF PET/CT scanner, compared non-TOF and TOF images on a large dataset of 100 oncology patients. An initial phantom study aimed to determine the iteration numbers that optimized the noise/contrast trade-off. Phantom images of lesions of different size and very low contrast ratio (2:1) were presented. Only TOF reconstruction allowed visual detection of the smallest lesion (10 mm). The SNR gain increased with BMI (Fig. 6), indicating that the improved SNR resulting from the use of TOF also increases with patient size, as expected. Qualitative evaluation by nuclear medicine experts confirmed the superior quality of the TOF images and also faster convergence and better contrast/noise trade-off.

Murray et al. [25] recently explored the possibility of reducing a patient's injected dose in a TOF PET scanner. Phantom and patient list-mode data were acquired on a Philips Gemini TF PET/CT. In order to simulate a reduced dose, full-dose and full acquisition time examinations were performed. The full list-mode data files were split into smaller files corresponding to reduced dose scans. The study included 20 whole-body PET/CT scans, 2 min per bed position, with injection of an average of 350 MBq ^{18}F-FDG. The 2-min TOF images were compared to 1-min, 30-s and 15-s images. The analysis of large areas of FDG uptake (>2 cm) showed a very good correlation between SUV measured with 2-min scans and the SUV measured with the shorter scans. Similar conclusions can be inferred from the phantom study with hot spheres of different sizes in which TOF and non-TOF reconstructions were performed, but a meaningful comparison was difficult, since two different algorithms were used for the TOF and non-TOF reconstructions: TOF-OSEM and non-TOF RAMLA. Nevertheless, the study showed that TOF and non-TOF reconstructions

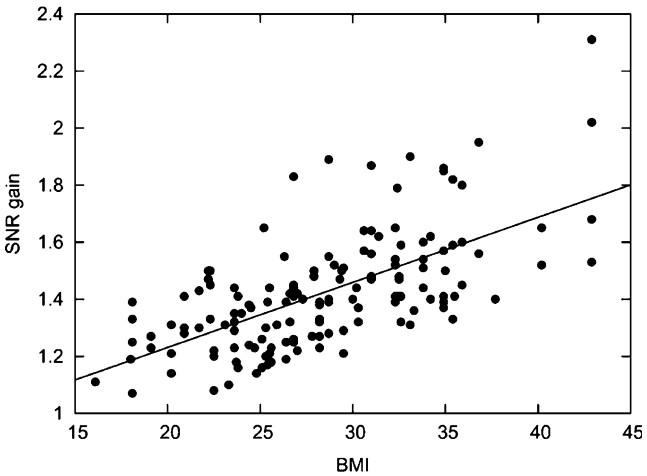

Fig. 6 SNR gain due to TOF vs. BMI for small tumoral lesions (<2 cm) selected in 100 oncology patients (from reference [35])

produced the same contrast recovery for large objects (hot spheres larger than 2 cm), but there was better contrast recovery in the TOF images for spheres 2 cm or smaller. Both phantom and patient studies agree that the lower level for acceptable images is 30 s, which implies the theoretical possibility of reducing the dose by a factor of up to 4 over the standard PET protocol.

While all previous studies were performed on LSO- or LYSO-based scanners, Daube-Witherspoon et al. [13] used the faster $LaBr_3$ on a TOF PET/CT scanner developed at the University of Pennsylvania. This performance of the TOF PET scanner was characterized by excellent time resolution (375 ps) and energy resolution (7%). In a phantom study with 10 mm high activity spheres in a lower activity background, TOF resulted in a dramatic improvement in contrast recovery and faster convergence. Plots of contrast recovery vs. noise at different total counts also showed that TOF reconstruction can be interpreted as a sensitivity amplifier: similar curves were obtained both by increasing the counts in the scan and by adding TOF mode. A 40-cm uniform phantom with six hot spheres (6:1 contrast ratio) located at different radial positions was also evaluated. The data were simulated with time resolutions of 650 ps and 375 ps. A decreased local variability was measured in TOF images, and the variability decreased further with the reduction in time resolution from 650 ps to 375 ps. This indicates a reduced disuniformity in the image: TOF suppresses both the effect of systematic and statistical noise.

Overall, there is clinical evidence that the TOF modality is equivalent to a sensitivity amplifier in terms of SNR [13]; that the improvement is greater with better time resolution [13]; that TOF reconstruction converges more quickly if an iterative algorithm is used [13, 33, 35]; that TOF offers better contrast recovery at the same noise level (or lower noise at same recovery level) [13, 33, 35] and better detection of small lesions [34]; and that the SNR gain is greater with larger patient size [33, 35]. In particular, the benefits of TOF reconstruction are larger under more challenging scanning conditions: shorter scans or low counts [13], larger patients [33, 35], low SUV or contrast [25], and smaller lesions [33, 35].

Towards improved time resolution

The benefits of TOF PET over conventional PET discussed in the previous section directly or indirectly derive from the TOF gain (in SNR or NEC) as expressed in Eq. 2, and could become larger if better time resolution could be achieved in the clinical environment. The present generation of commercial TOF PET scanners has a time resolution in the range 500–600 ps, but there is space for improvement in the coming years. A time resolution of 300 ps, for example, could improve TOF SNR by a factor of 3 over non-TOF, and improve equivalent counts by a factor of 9, as can be seen in Table 1.

The benefits of improved image quality are shown in Fig. 7 with a Geant4 Monte Carlo simulation of a TOF PET tomograph based on the architecture of the Siemens mCT TOF PET scanner [10]. The phantom was a 30-cm diameter uniform water cylinder with uniform background activity and with six spheres. The smallest spheres (10, 13, 17 and 22 mm diameter) were filled with ^{18}F water solution at a contrast ratio of 4:1, and the two larger spheres (28 and 37 mm diameter) were filled with water and no activity. No scatter or attenuation were assumed, and filtered back-projection was used for reconstruction. The transaxial slices had a 4 mm pixel size. Two datasets with a time resolution of 300 ps and 600 ps were simulated, and for each dataset, a non-TOF and a TOF reconstruction with corresponding TOF kernel were used. A high statistics case (356×10^6 counts on the whole volume of 109 planes) and a low statistics case (10×10^6 counts) were compared.

Figure 7 shows that, if high statistics data are available, TOF reconstruction reduces the noise level with increasing time resolution, but the improvement is dramatic if low counts data are used. In the low statistics example, the 10-mm sphere was not visible in the non-TOF image, it was hardly visible over the noise pattern if 600-ps TOF reconstruction was used, but it was clearly identified in the 300-ps TOF image. This is of particular interest, since the low statistics is the most common situation in clinical practice, where 1–3 minutes per bed position are typically acquired.

A dramatic improvement of the system time resolution can be achieved by a careful review of the many technological factors that contribute to the time resolution of a TOF PET scanner [4, 36]. Some are related to the choice and the design of the components, others to quality and uniformity of the components. In the present generation of TOF scanners, the main components typically are: an inorganic crystal that converts the high-energy photons into visible light photons, a light sensor and amplifier such as the photomultiplier tube (PMT), and the associated electronics for shaping, amplification, discrimination and time stamping. The scintillator material characteristics could be the first constraint to time resolution in terms of rise time, decay time and absolute light output. In fact, since the intrinsic time resolution of the present TOF PET scintillators (LSO, LYSO and $LaBr_3$) are in the order of 100–200 ps [37, 38], the scintillator itself does not appear to be a limitation for achieving better system time resolution. The geometry of the scintillator crystals has an effect on time resolution. Typically, crystals have small cross sections for good position identification and long lengths to provide good detection efficiency. A light guide is used to interface

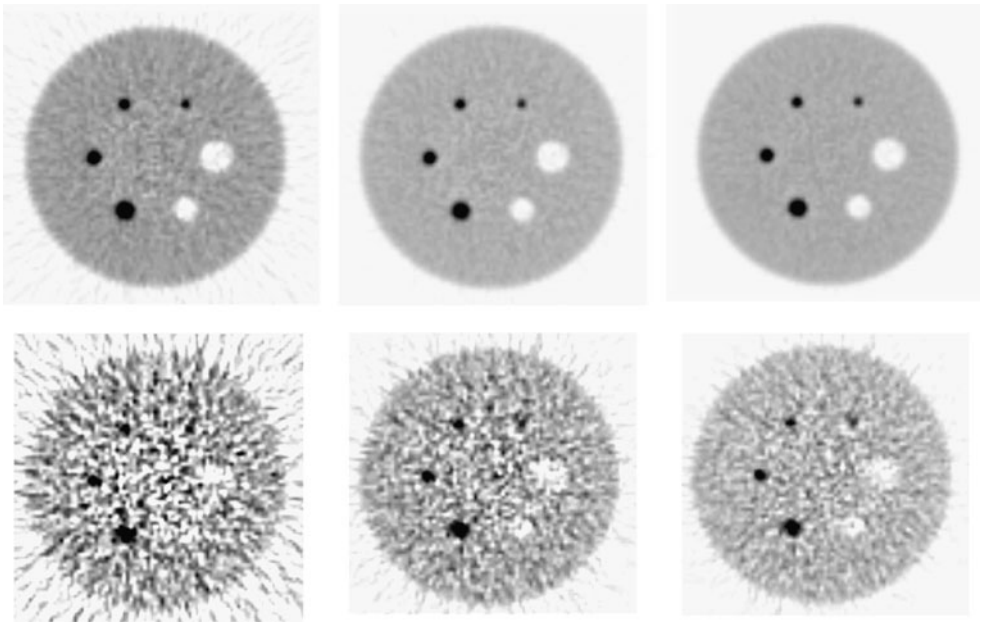

Fig. 7 Monte Carlo simulation of a uniform cylinder with spheres of diameter 10, 13, 17 and 22 mm at a contrast ration of 4:1 and two spheres of diameter 28 and 37 mm filled with water with no activity: high statistics, 356×10^6 counts in the total volume (*top*); low statistics, 10×10^6 counts (*bottom*). Filtered back-projection was used for non-TOF reconstruction (*left*), for TOF reconstruction with 600 ps time resolution (*centre*), and for TOF reconstruction with 300 ps time resolution (*right*)

crystals with the PMTs. Several reflections of light in the crystals and light guide and the length of the crystal itself create path length dispersion and hence travel time dispersion, which affect time resolution. Light losses in the crystals and light guide, or at the boundaries, also create anisotropic differences in the number of visible photons, affecting the time resolution. Careful redesign of the detector units and the optics could improve time resolution.

The photodetector used, the PMT, contributes to the broadening of the time resolution. The sensitivity and the transit time depend on the position of the incident light photon on the face of the PMT. There are also variations in the hundreds of PMTs used in a PET system. Presently, special interest is directed towards silicon photomultipliers (SiPM) as a possible replacement for PMTs [39, 40]. These devices are based on a large number of small (30–100 μm size) avalanche photodiodes working in Geiger mode. The number of the cells that discharge, each producing the same signal, is proportional to the light quanta detected. SiPMs require a much lower bias than PMT (<100 V), are insensitive to magnetic fields, are very compact in size, and have an amplification similar to that of PMTs (around 10^6). Recent measurements have showed that SiPM have the potential to perform as well as or better than PMTs in terms of timing [41, 42], but some issues still have to be addressed: a good balance needs to be found between dead space between the cells and saturation at high count rate, dark current must be reduced in order to obtain good size devices with low noise, and cost must be reduced.

Finally, the processes of triggering, shaping, amplification, discrimination and time stamping, and the electronic noise associated with all components and the layout of a complex system are factors that degrade time resolution. Particular attention must be given to discrimination and time stamping of the signal.

Conclusions

TOF PET has only recently become available for use in a clinical environment. Nevertheless, there is already evidence published in the scientific literature of the benefits of TOF over conventional (or non-TOF) PET in a clinical setting. TOF reconstruction offers a better trade-off between contrast recovery and noise (or better SNR), shows better detection of small lesions, and performs better at very low statistics.

The following are advantageous characteristics of TOF PET:

- The TOF gain is greater for large patients, whose scans are usually characterized by compromised image quality.
- The virtual counts amplification of TOF reconstruction can open the way for dose reduction at the same image quality.
- Alternatively, the examination time can be reduced with better patient workflow and patient comfort.
- The lower noise allows the use of smaller image voxels, exploiting the spatial resolution limits of the PET scanner.
- The additional TOF information can be used to overcome artefacts due to missing data, and new dedicated PET scanners with challenging geometries may also benefit from TOF reconstruction.

In particular, the benefits of TOF reconstruction are larger under more challenging scanning conditions, and

include shorter scans or low counts, successful scanning of larger patients, low SUV or contrast, and visualization of smaller lesions.

Since the advantages of TOF PET are directly related to the time resolution of the PET scanner, there is great interest in further improving the time resolution of the present generation of TOF PET scanner. A sizable advance can only be achieved with combined optimization of the main components, in particular optics, photodetectors and electronics.

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Conflicts of interest None.

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