Limited-angle TOF-PET for intraoperative surgical applications: proof of concept and first experimental data

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Abstract: The intraoperative gamma probe (IPG) based on single gamma-ray detection remains the current gold standard modality for sentinel lymph node identification and tumor removal in cancer patients. However, IPGs do not meet the < 5% false negative rate (FNR) requirement, a key metric suggested by the American Society of Clinical Oncology (ASCO). We aim to reduce FNR by using time of flight (TOF) PET detector technology in limited angle geometry system by using only two detector panels in coincidence. For proof of concept, we used two Hamamatsu TOF PET detector modules (C13500-4075YC-12) featuring 12 × 12 arrays of 4.14 × 4.14 × 20 mm³ LFS crystal pixels with 4.2 mm pitch and coupled one-one to silicon photomultiplier (SiPM) pixels. The measured detector coincidence timing resolution (CTR) was 271 ps FWHM for the whole detector. We 3D printed lesion phantom containing spheres 2–10 mm in diameter, representing lymph nodes, and placed it inside a 10-liter warm background water phantom. Experimental results showed that with subminute data acquisition, 6 mm diameter spheres could be identified in the image when a lesion phantom with a 10:1 activity ratio to background was used. The simulation results were in good agreement with the experimental data by resolving 6 mm diameter spherical lesions with a 60 second acquisition time in a 25 cm deep background water phantom with a 10:1 activity ratio. As expected, the image quality improved as the CTR improved in the simulation and with decreasing background water phantom depth or increasing lesion-to-background activity ratio in the experiment. With the results presented here, we concluded that using a limited angle TOF PET detector system is a major step forward for intraoperative applications in that lesion detectability is beyond what conventional gamma- and NIR-based probes could achieve.

Keywords: Gamma camera, SPECT, PET PET/CT, coronary CT angiography (CTA); Gamma detectors (scintillators, CZT, HPGe, HgI etc); Intra-operative probes; Timing detectors

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1 Introduction

Intravenous (IV) injection of $^{18}$F-fludeoxyglucose (FDG) and positron emission tomography (PET) imaging using a clinical scanner are considered standards in tumor detection and disease staging for cancer patients. However, it has been shown that this approach is only reliable for detecting tumors larger than 1 cm using a conventional whole-body PET (WB-PET) scanner; thus, with this approach, small-size tumors and cancerous lymph nodes are often missed [1]. The key reasons for this poor diagnostic power are the relatively low spatial resolution (4–5 mm FWHM), low standardized uptake value (SUV) associated with $^{18}$F-FDG, and inherently low sensitivity (~ 1%) of a conventional WB-PET scanner. These limitations have led to the development of intraoperative devices where detectors are placed close to the tissue of interest to increase the solid angle and, hence, improve the detection efficiency.

The sentinel lymph node (SLN) concept is based on the orderly progression of tumor cells within the lymphatic system. The SLN will be the first to contain metastasis, and biopsy will accurately predict regional nodal status [2]. The current standard of care for breast cancer patients is to use both injection with blue dye (followed by direct visual inspection during surgery) and peritumoral injection of radiopharmaceuticals for intraoperative identification of SLNs using a gamma probe [3–8]. It has
been shown that histological evaluation of one or more SLNs increases the accuracy of histopathologic staging of the axilla in patients with breast cancer. Histological examination of LNs is important in determining metastatic involvement; however, this examination requires node dissection and is associated with immediate and late postsurgical complications, especially lymphedema [9]. It should be noted that a thorough histological evaluation of 5 or more nodes is impractical, or even impossible, in the current standard of care [10]. Additionally, the number of sections per node undergoing histological examination is limited (typically < 4), which can lead to undersampling of the involved nodes [11, 12]. Furthermore, the SLN identification approach has a significant false negative rate associated with cancer cells that pass to downstream in the lymphatic system, causing the cancer nodes to be missed [13]. Guidelines from the American Association of Clinical Oncology (ASCO) [14] state that surgical practices should aim for an 85% identification rate and less than 5% false negative rates (FNRs), which is not met by the current standard of care using gamma probes and near infrared probes [15]. This gap indicates that there is an unmet clinical need for tools that allow efficient and accurate examination of a sufficiently large number of nodes intraoperatively before resection.

While there is a large body of research conducted in different oncological applications, SNL identification is currently used as the standard of care in breast and skin cancer patients. The most commonly used technology to identify SLNs is the gamma probe, which, as mentioned above, is associated with a relatively high false negative rate. The detection sensitivity of these devices is also dependent on the tumor location, and their performance is poor near the injection site and in deeply positioned tumors. Another factor that hampers the usefulness of the gamma probes is that they cannot provide depth information unless they are rotated with respect to the FOV in multiple angular positions to estimate tissue depth.

The other alternative in radiation-based intraoperative identification of SNL is the use of short-range positron particles from PET tracers such as FDG. There is a large body of work dedicated to the development of positron probes for intraoperative use [16–23]. Note that compared with intratumoral injection of $^{99m}$Tc colloids, the benefits of IV injection of FDG, which can be used for both preoperative and intraoperative imaging, could justify the higher patient dose. However, a higher occupational dose of 18F-FDG may be considered a drawback [24].

The advent of time of flight (TOF) PET has shown great promise in increasing image signal-to-noise (SNR) and patient dose reduction [25–27]. Commercially available TOF-PET systems with high coincidence timing resolution (CTR), where the most recent developments reach down to $\sim$200 ps, have enabled high-quality PET imaging, and diagnostic PET imaging with limited angle detector coverage is an active area of research [26]. Encouraged by these developments, this work explores the implementation of TOF-PET for intraoperative imaging as a strong alternative to intraoperative gamma probes, positron probes, 3D gamma cameras [28], and preoperative dedicated PET scanners [29, 30]. Here, we lay down our recent proof of concept work for intraoperative TOF-PET with simulations and pilot experimental data.

2 Materials and methods

2.1 Simulation setup

In our recent work, we have shown through Monte Carlo simulation using GATE (GEANT4) that by bringing detector modules close to the patient, the detector solid angle and thus the geometrical
sensitivity rapidly increases even with a small number of detector modules [16, 31]. Our previous studies showed that by using ~ 1/3rd of the detector modules from a whole-body PET and rearranging them in a limited-angle body-contouring configuration (see figure 1), system sensitivity and resolution can be preserved [16, 31]. With these encouraging initial results, we further included flat panel detector geometries where the detector modules were placed in two parallel planes one right above the patient body and one below the surgery bed.

![GATE renderings of a series of PET system geometries showing the evolution from WB-PET to limited angle intraoperative PET.](image)

**Figure 1.** GATE renderings of a series of PET system geometries showing the evolution from WB-PET to limited angle intraoperative PET. a) A whole-body PET with a 76 cm bore diameter and 15 cm axial length. There were 44, $5.1 \times 5.1$ cm$^2$ detector modules per ring and 3 rings in the gantry, totaling 132 modules. b) Only the bottom half of the WB-PET ring in coincidence with a $15 \times 15$ cm$^2$ detector panel placed close to the patient. The total module number was 75 ($9 + 132/2$). c) First schematic of a possible intraoperative PET configuration with $8 \times 3$ modules under the patient and $3 \times 3$ modules above the patient (total 33 modules). d) Intraoperative PET in (c) evolved into a geometry with increased detector coverage while maintaining a small footprint above the patient where the surgical procedure takes place. In (d), there are 40 ($8 \times 5$) and 9 ($3 \times 3$) detector modules under and above the patient, respectively (total of 49) [31].

In this work, we conducted a proof-of-concept phantom experiment along with Monte Carlo simulations of a practical first configuration consisting of commercially available TOF-PET detector technology from Hamamatsu Photonics used in a dual flat panel detector configuration. The simulation setup models C13500-4075YC-12 TOF-PET detectors (Hamamatsu Photonics, Japan). Each detector module is comprised of a $12 \times 12$ array of $4.14 \times 4.14 \times 20$ mm$^3$ lutetium fine silicate (LFS) crystal pixels with 4.2 mm pitch one-one coupled with silicone photomultiplier (SiPM) pixels. The overall active area of the detector module is $51 \times 51$ mm$^2$. The external dimension of the module, including light-tight housing, is $53 \times 53$ mm$^2$. Figure 2 shows the demo unit used in the experimental and simulation setup.

### 2.1.1 Phantom

A rectangular container measuring $24.5 \times 13.5 \times 25$ (L × W × H) cm$^3$ was simulated as a slice of the patient body within the scanner FOV. The container was filled with 5.3 kBq/cc with a back-to-back gamma source. The background tracer concentration is based on a 10 mCi injection of $^{18}$F-FDG into a 70 kg human. Hot spheres with 2, 4, 6, 8, and 10 mm diameters in two rows with 10:1 tracer uptake compared to the background represent tumors and lymph nodes. The $^{18}$F activities of the hot spheres were calculated at 222, 1776, 5994, 14208, and 23790 Bq. Center-to-center distances between the hot spheres were kept at 1 cm. Hot spheres were positioned in the rectangular phantom.
with their centers positioned 2 cm below the phantom surface. A GATE render of the hot lesion phantom is shown in figure 3 (bottom-right).

2.1.2 Detector placement and data acquisition

We simulated two detector panels with different numbers of detector modules per panel. In the first study, the detector panel placed atop the patient contained only two modules, while the panel underneath the patient bed contained a $3 \times 3$ array of modules of the same size. The number of detectors per panel is selected based on the acquisition time limitations that we faced with only having two Hamamatsu TOF-PET detectors and the use of short half-life $^{18}$F isotopes. The face-to-face distance between the two detector panels was 27 cm to be large enough for a 25 cm thick phantom representing an average person torso and an approximately 2 cm bed structure (the bed material was not simulated). Simulations were performed across 20 CPU threads with 9 seconds per thread using a random engine with automatic seed. Detectors were modeled with 191 ps single module time blurring resulting in 271 ps CTR and 16.7% energy blurring to be consistent with the measured values (see sections 2.2.6 and 2.2.7) for the Hamamatsu TOF-PET detectors.

2.2 Experimental setup

2.2.1 TOF-PET detector modules

The experiments reported in this paper are based on a TOF-PET demo unit from Hamamatsu, which includes two C13500-4075YC-12 detector modules, a clock distribution board, a power supply board, a relay board, a PCIe interface board, and associated cables. Each of the two detector modules is comprised of a $12 \times 12$ array of $4.14 \times 4.14 \times 20 \, \text{mm}^3$ LFS crystal pixels with a 4.2 mm pitch, one-to-one coupled to SiPM pixels with 75 μm microcells [1]. The overall dimension of the detector module is $50.4 \times 50.4 \, \text{mm}^2$. Eight 18-Ch ASIC chips in the front-end electronic board process the SiPM signals and pass the signal to downstream electronic boards. The ASICs use the
time-over-threshold (ToT) technique for extracting time and energy information. Similar TOF-PET modules were recently evaluated [32–34] for diagnostic PET applications. A photo of the demo unit provided by Hamamatsu Photonics is shown in figure 2.

It should be noted that we replaced the 15 cm long cables in the demo unit connecting the two detector boards to the timing PCB with 100 cm cables to increase the detector-to-detector distance enabling more realistic experimental scenarios.

2.2.2 Phantom

In the experimental setup, we used stackable water containers with $24.5 \times 13.5 \text{ cm}^2$ base dimensions and the possibility to accommodate water depths up to 25 cm. This maximum thickness (water depth) was selected based on the outer diameter of torso shape IQ phantom described in NEMA standard [35] representing an average human torso. The base dimensions extended slightly outside the FOV. We assumed that further out-of-FOV activity can be shielded in real applications. We 3D printed multiple hot sphere phantoms using clear resin with a Form3 printer (Formlabs, U.S.A.), as shown in figure 3. To make the hot spheres fillable, we implemented 0.6 mm diameter channels to connect spheres within the phantom to the phantom’s top surface. To verify hot sphere dimensions, the volume inside each sphere was measured after printing with a precision 10 μl syringes for small spheres up to 1000 μl syringes (Hamilton, U.S.A.) for larger spheres. The spheres printed with inner diameter of 9.5, 8, 6, 4, and 2 mm and the measured volume of liquid shows spherical volumes with 9.36, 7.82, 5.66, 3.72, and 1.75 mm. The measured diameters will be considered as the actual lesion diameter in this study. To experimentally investigate the effect of the tracer-to-background ratio on the image quality, three phantoms were filled with 5:1, 10:1, and 20:1 intended activity ratios compared to the background. Note that for better visualization, the radiotracer was mixed with food.
coloring prior to phantom filling. For each experiment, after filling the spheres, the channels were sealed using epoxy sealant. We used $^{18}$F to fill the water container and the hot sphere phantoms. The water container was fixed on a set of construction rails (Thorlabs, U.S.A.). This fixture was mounted on a Velmex BSilde (Velmex, U.S.A.) vertical motorized stage to control the position of the water tank and the lesion phantom with respect to the coincidence detector modules. We 3D printed a lesion phantom holder to place the hot sphere phantom in different vertical positions inside the water container and then moved the container vertically to place the lesion phantom in its intended position with respect to the top detector module. Radioactive water was removed or added to the containers to reach desired water levels using a small water pump and a valve. A GATE rendering of the phantom along with photographs of the experimental setup are also shown in figure 3.

2.2.3 Experimental procedure

Given the availability of only two TOF-PET detector modules in the demo unit, we mounted one detector module on a horizontal bar atop the rectangular water container and the other module on an X-Y BiSlide motorized stage (Velmex, U.S.A.). The top detector can be manually moved in two positions to represent a $5.1 \times 10.2$ cm$^2$ detector area. Note that the two positions were selected to cover the hot sphere phantom with enough line of response (LOR) sampling and to avoid long acquisition time imposed by relatively short decay of $^{18}$F. The bottom detector was moved in a $3 \times 3$ position map, providing $15.3 \times 15.3$ cm$^2$ detector coverage. Data acquisition was repeated for a total of $2 \times 9$ detector positions, where for each top detector position, the bottom detector was moved in step and shoot mode, and data were acquired for each detector position. The resulting 18 datasets were scaled in time for decay correction to arrive at a fixed effective scan time. This setup allowed us to mimic a complete detection system where data would be acquired simultaneously with all detector combinations.

Figure 4. Photograph of the calibration setup used in uniformity, energy, and timing corrections. A 2D scanning stage holds the bottom detector module, while the two-position sliding posts hold the top detector module. At the center plane between the two detectors, the phantom is placed to collect a large number of coincidence events for corrections.
For the main experiment, we scanned the lesion phantom with a 9.1:1 lesion-to-background ratio in 180 seconds for each of 18 detector position combinations (2 positions for the top detector and 9 positions for the bottom detector). The overall data acquisition took 61 minutes, including detector module repositioning for all 18 positions while in a setup with fully populated detector modules, data acquisition would take under 3 minutes. Note that the effective scan time corresponds to the total scan time if all 18 detector positions had been populated. The decay correction was implemented by having the 18th position as the reference and cutting the coincidence counts from the acquired data for position steps 1st to 17th, the data acquisition times used for image reconstruction, ranged from 125 s for the first detector position to 180 s for the 18th position.

Further to illustrate the effect of the timing resolution of the detector modules, we compared the simulation result of a detector system with 271 ps FWHM CTR to that of a 100 ps.

To investigate the effect of the uptake ratio on the image quality, we carried out experiments with a fixed 60 second acquisition time and with 4.5:1, 9.1:1 and 18.9:1 lesion/background uptake ratio phantoms. All measurements were performed on the same day, and thus, the activity at the end of each experiment was different. Therefore, we trimmed all experimental data according to the activity of background water at the end to the shortest scan, which was the one with a 4.5 uptake ratio.

In addition, to see the impact of the scattering media on the image quality, we performed measurements using the 9.1:1 phantom with different background water depths. For this purpose, the background water level in the container was adjusted to the desired level, while the lesion phantom was maintained at a fixed depth 2 cm below the water surface. Note that the containers were then moved with respect to the detectors to keep the distance between the water surface and the top detector constant throughout all experiments. The distance between the two detector panel planes was fixed. Similarly, we trimmed experimental data according to the activity of background water at the end of each step to the shortest collected data point.

2.2.4 Uniformity phantom

To calibrate the two detector modules for timing, energy, and uniformity, we 3D printed a uniformity phantom with the same size of detector modules placed at the center of the hypothetical line connecting the coincidence detectors. Figure 4 shows the uniformity phantom and data acquisition setup. Coincidence data were collected for 7 hours while we maintained the event count rate in both detector modules to be less than 3 Mcps by adding more 18F solution to the phantom every ~ 45 minutes.

2.2.5 Coincidence filter

As part of the demo unit kit, data collection software was provided to read raw data with direct memory access (DMA). The raw data for each event are packed in 16 bytes and contain absolute event arrival time with 15.0602 ps resolution (47 bits), energy in ToT (8 bits), and board/crystal ID (17 bits).

For the coincidence filter, the raw data collected in list mode should be sorted based on the time stamp. Since the amount of raw data for the uniformity calibration was more than 600 GB, we implemented 12 stages of the fast swapping technique presented in [36] for fast sorting of raw data in the coincidence filter. Based on this method, we have also implemented a delayed coincidence filter for correcting random coincidences. A delayed window with a 100 ns offset was created for the delay coincidence filter.
Figure 5. Map of the photopeak position for each of the 144 scintillator pixels of the two detector modules. After energy correction for the two detectors, an energy resolution of 16.7% was achieved.

Figure 6. Time offset between each crystal pair of the two detector modules a) before and b) after correction with 271 ps FWHM CTR.

2.2.6 Energy correction

In the first stage of data processing, energy correction is required to set the energy window and avoid including scatters and spurious events in the detectors. In practice, we noticed that the detector modules are configured at a very low threshold for registering counts to maintain high timing performance; therefore, the rate of spurious events is higher than in conventional non-TOF detectors. For energy correction, we used coincidence data from the acquired uniformity calibration data and obtained energy spectra for each crystal-SiPM pair on the ToT scale. Then, we used the channel correction factor to overlay photopeak centers in all single crystal-SiPM pairs. We used the parameters presented in [32] to convert the ToT value to the keV value to set the energy window on the keV scale instead of the ToT scale. Figure 5 shows the energy peak map of detector pixels in two detector modules. After overlaying photopeaks in the same dataset, the energy resolution of detector modules was calculated at 16.7% full-width at half-maximum (FWHM).

2.2.7 Timing correction

Since there is only a minimal amount of scattering media in our uniformity phantom, we used a wide energy window to acquire coincidence data and plot them as $144 \times 144$ values to find the time offset for each crystal pair. We used these data to correct timing differences between crystal pairs. Figure 6a shows the time offset between each detector pixel pair in the two detector modules. The vertical axis is in picoseconds. Note that the cable length between the detector modules to the coincidence
unit was different in that the cable length for module 1 was 15 cm and that for module 2 was 100 cm, which led to an ~ 2.4 ns arrival time difference. Figure 6b shows the timing plot for the two detector modules after correcting timing offsets for different pixel pairs with 271 ps FWHM CTR.

2.2.8 Uniformity correction

Uniformity correction was performed based on the same data collected for timing correction after we stored each detector pair count in a 144 × 144 matrix as the reference for uniformity correction with an average of 645 counts per pair (total of ~ 13.4 M coincidence counts).

2.3 Image reconstruction and quality evaluation

2.3.1 Image reconstruction

While acknowledging the superior performance of iterative and statistically based image reconstruction methods, we have implemented a simple 3D back-projection method with TOF information for simplicity, to meet the requirement of on the fly image reconstruction and to provide a display in intraoperative applications [16]. In this method, we back-projected a Gaussian curve with 271 ps plus crystal thickness FWHM into the image matrix. Despite the well-known filtered back-projection method in 2D image reconstruction, we did not use the ramp filter because of the irregular shape of the geometry and FOV. The image matrix comprised 256 × 256 × 256 voxels, with each voxel representing a 1 mm³ volume. However, the small image voxel with respect to 4.2 mm detector pixels leads to speckle artifacts in the reconstructed image and requires incorporation of a point spread function into the back-projection. To mitigate this effect, we employed oversampling of the interaction position in two directions across the detector pixel surface [16]. The oversampling is more precise than simple Gaussian blurring, where the detector orientation can be arbitrary, but on the other hand, the computation time increases linearly by the oversampling factor in the X and Y directions, which can be minimized by employing a GPU instead of a CPU. In all reconstructed images in this work, we used a 10× oversampling factor in each dimension of the crystal pixel surface, creating 100 LORs from one LOR in the list-mode data. Image reconstruction was performed using a single CPU core. As the current simple image reconstruction method is used for proof of concept, further work is required to fully investigate the effect of different image reconstruction methods for this geometry and intraoperative application.

2.3.2 Image quality metrics

After reconstruction, we evaluated the image quality using the contrast recovery coefficient (CRC), signal-to-noise ratio (SNR), and contrast-to-noise ratio (CNR). CRC is described in the NEMA standard [35] to measure the quality of hot rods in the scan of micro-Derenzo phantoms. It represents how much of the real activity is actually recovered in the reconstructed image. We modified the CRC to reflect the use of hot spheres instead of rods (with no slice summation) as follows:

\[ \text{CRC} = \frac{\text{Mean}_{\text{HotSphere}}}{\text{Mean}_{\text{Background}}} - 1 \]

\[ = \frac{\text{Activity}_{\text{HotSphere}}}{\text{Activity}_{\text{Background}}} - 1 \]

where “Activity” refers to the activity of the phantom and background in the same region of interest (ROI) where the “Mean” is calculated. CNR shows the detectability of the hot spheres and is defined
as the ratio of the image contrast to the noise in the background:

$$\text{CNR} = \frac{\text{Mean}_{\text{HotSphere}} - \text{Mean}_{\text{Background}}}{\text{Std}_{\text{Background}}}$$

and SNR is calculated using:

$$\text{SNR} = \frac{\frac{\text{Mean}_{\text{HotSphere}}}{\text{Mean}_{\text{Background}}} - 1}{\sqrt{\left(\frac{\text{Std}_{\text{HotSphere}}}{\text{Mean}_{\text{HotSphere}}}\right)^2 + \left(\frac{\text{Std}_{\text{Background}}}{\text{Mean}_{\text{Background}}}\right)^2}}$$

where “Std” refers to the standard deviation of pixel values. The ROI for the hot spheres is obtained based on the accurate alignment of the phantom and detectors and not from the pixel values. For the background, we used two circular shapes with a 15 mm diameter in the same image plane with center coordinates at 40 mm and −35 mm from the center of the FOV at the horizontal axis and center at the vertical axis (see figure 7). For the hot spheres, the parameters for each of the two spheres with the same size are calculated separately, and the mean and standard error of two values are calculated. Since the two smaller sphere sizes are not visualized and the parameters do not represent a meaningful value to compare, here we report on sphere sizes of only 5.7 mm, 7.8 mm, and 9.4 mm.

![Figure 7. Delineation of ROIs as cutoffs in the image for hot spheres with diameters 2–10 mm and two circular background regions with 15 mm diameter all in the same image plane.](image)

3 Results

The image matrix size in image reconstruction is 256 × 256 with a 1 mm size in all directions. All reconstructed images of the plane containing the hot lesion spheres are shown in coronal view to be most consistent with the surgeon view in an intraoperative procedure.

In the main study we obtained experimental results for 180 s effective scan time and compared this result with those obtained for simulation with the same scan time and activity. The background and lesion activity concentrations at the last step of the experiment were 0.052 μCi/ml and 0.47 μCi/ml, respectively, which was set for the simulation as well. After applying energy, TOF, uniformity, and sensitivity correction or the experimental data and sensitivity correction for simulated data, results are shown in figure 8 and table 1.

The effect of the different timing performance of the detector block is investigated using the simulation platform and figure 9 shows the image quality improvement due to the better CTR as manifested by clearly resolved 6 mm Dia. spheres well above the background noise in the line profile. Image quality metrics are presented in table 2.
Figure 8. Experimental (a) and simulation (b) results of the lesion phantom with an $\sim 10 : 1$ lesion to background activity in 25 cm background water. c) shows the horizontal line profile through the upper line of the hot spheres in the lesion phantom. Effective scan time was 180 s in 25 cm background water activity with 0.047 $\mu$Ci/ml at the start of the last step. Note that the effective scan time corresponds to the total scan time if all 18 detector positions had been populated. The reported activity concentrations are at the time of data acquisition of the last step.

Table 1. Image quality parameters comparing the simulation and experimental study. The lesion-to-background activity ratio was $\sim 10 : 1$, the CTR was 271 ps, and the background water depth was 25 cm in both studies. Sphere diameters in parentheses correspond to simulations. Note that spheres with Dia. $< 5$ mm cannot be visualized and therefore their data is not shown here.

| Sphere Diameter (mm) | 9.4 (10) | 7.8 (8) | 5.7 (6) |
|----------------------|----------|---------|---------|
|                      | Experiment | Simulation | Experiment | Simulation | Experiment | Simulation | Experiment | Simulation |
| CNR                  | 5.052 ± 0.003 | 4.084 ± 0.073 | 2.146 ± 0.239 |
|                      | 16.502 ± 0.037 | 12.412 ± 0.754 | 7.1 ± 0.467 |
| CRC                  | 0.067 ± 0.001 | 0.054 ± 0.001 | 0.029 ± 0.003 |
|                      | 0.086 ± 0.001 | 0.065 ± 0.004 | 0.037 ± 0.002 |
| SNR                  | 0.033 ± 0.001 | 0.034 ± 0.002 | 0.019 ± 0.001 |
|                      | 0.475 ± 0.141 | 0.375 ± 0.019 | 0.303 ± 0.009 |
Figure 9. Simulation results showing the impact of a) 100 ps CTR on image quality compared to b) 271 ps FWHM CTR detector. The corresponding line profiles are shown in c). Effective scan time was 180 s in 25 cm background water with activity of 0.047 μCi/ml at the start of the last step.

Table 2. Image quality parameters comparing the timing resolution effect. Images were obtained through simulations with a 10:1 lesion-to-background activity ratio and 25 cm water depth. Spheres with Dia. < 6 mm cannot be visualized.

| CTR Value | Sphere Diameter (mm) | 10       | 8        | 6        |
|-----------|----------------------|----------|----------|----------|
| 100 ps    | CNR                  | 21.451 ± 0.556 | 16.136 ± 1.019 | 8.832 ± 1.139 |
| 271 ps    | CNR                  | 16.037 ± 0.163 | 12.412 ± 0.754 | 7.1 ± 0.467   |
| 100 ps    | CRC                  | 0.161 ± 0.003  | 0.121 ± 0.008  | 0.066 ± 0.009 |
| 271 ps    | CRC                  | 0.086 ± 0.001  | 0.065 ± 0.004  | 0.037 ± 0.002 |
| 100 ps    | SNR                  | 0.713 ± 0.177  | 0.533 ± 0.083  | 0.395 ± 0.044 |
| 271 ps    | SNR                  | 0.475 ± 0.141  | 0.375 ± 0.019  | 0.303 ± 0.009 |
The effect of lesion to background ratio is summarized in figure 10 and table 3. The results show the image quality and parameters for 3 uptake ratios. As expected, the phantom with a higher uptake ratio resulted in better image quality.

![Figure 10](image1.png)

**Figure 10.** Experimental results showing the impact of the lesion-to-background ratio on image quality when using flat panel PET detectors with 271 ps FWHM CTR. Lesion to background ratios of 18.9, 9.1, and 4.5 are shown in a), b), and c), respectively. Superimposed line profiles are shown in d). Effective scan time was 60 s in 25 cm background with activity of 0.078 μCi/ml at the start of the last step.

**Table 3.** Image quality parameters comparing the lesion to background ratio (LBR). Images were obtained through experiments with a 25 cm water depth and 271 ps CTR. Spheres with Dia. < 5 mm cannot be visualized.

| LBR | Sphere Diameter (mm) |         |         |         |
|-----|----------------------|---------|---------|---------|
|     | 9.4                  | 7.8     | 5.7     |         |
| 4.5 | 0.897 ± 0.485        | 1.37 ± 0.059 | N/A     |         |
| CNR | 9.1                  | 5.168 ± 0.033 | 3.708 ± 0.163 | 1.637 ± 0.676 |
|     | 18.9                 | 7.404 ± 0.64 | 5.663 ± 0.394 | 2.372 ± 0.736 |
| 4.5 | 0.014 ± 0.008        | 0.022 ± 0.001 | N/A     |         |
| CRC | 9.1                  | 0.072 ± 0.001 | 0.052 ± 0.002 | 0.023 ± 0.009 |
|     | 18.9                 | 0.15 ± 0.013 | 0.115 ± 0.008 | 0.048 ± 0.015 |
| 4.5 | 0.004 ± 0.002        | 0.005 ± 0.0 | N/A     |         |
| SNR | 9.1                  | 0.016 ± 0.001 | 0.016 ± 0.001 | 0.007 ± 0.003 |
|     | 18.9                 | 0.028 ± 0.003 | 0.023 ± 0.004 | 0.011 ± 0.003 |

The effect of different warm background water depth is depicted in figure 11 and table 4.
Figure 11. Experimental results showing the impact of background water depth on the image quality when using flat panel PET detectors with 271 ps FWHM CTR. Lesion phantom activity ratio is 9.1 and background water depth of 4.6 cm, 8 cm, 12 cm, and 25 cm are shown in a, b, c, and d, respectively. e) shows the superimposed line profile through one pixel row in the reconstructed images. Effective scan time was 60 s with background activity of 0.058 μCi/ml at the start of the last step.

Table 4. Image quality parameters comparing different background water depths. Images were obtained through experiments with a 9.1:1 lesion to background ratio and 271 ps CTR. Spheres with Dia. < 5 mm cannot be visualized.

| Depth (cm) | Sphere Diameter (mm) | 9.4 | 7.8 | 5.7 |
|------------|----------------------|-----|-----|-----|
|            | CNR                  |     |     |     |
| 4.6        | 9.416 ± 0.225        | 6.67 ± 0.098 | 2.586 ± 0.021 |
| 8          | 6.543 ± 0.141        | 4.224 ± 0.343 | 1.645 ± 0.166 |
| 12         | 5.374 ± 0.008        | 3.92 ± 0.281 | 2.122 ± 0.151 |
| 25         | 4.489 ± 0.045        | 3.015 ± 0.305 | 1.361 ± 1.072 |
|            | CRC                  |     |     |     |
| 4.6        | 0.137 ± 0.003        | 0.097 ± 0.001 | 0.037 ± 0.001 |
| 8          | 0.092 ± 0.002        | 0.059 ± 0.005 | 0.023 ± 0.002 |
| 12         | 0.088 ± 0.001        | 0.064 ± 0.005 | 0.035 ± 0.002 |
| 25         | 0.075 ± 0.001        | 0.05 ± 0.005  | 0.023 ± 0.018 |
|            | SNR                  |     |     |     |
| 4.6        | 0.073 ± 0.008        | 0.059 ± 0.004 | 0.026 ± 0.003 |
| 8          | 0.063 ± 0.002        | 0.048 ± 0.001 | 0.019 ± 0.003 |
| 12         | 0.036 ± 0.001        | 0.03 ± 0.001  | 0.017 ± 0.001 |
| 25         | 0.012 ± 0.001        | 0.01 ± 0.001  | 0.005 ± 0.004 |
4 Discussion & conclusion

We have demonstrated that the ready-to-use compact TOF-PET technology from Hamamatsu Photonics can be adapted to our intraoperative PET imaging concept. Using a two-module demonstration kit, we developed a step and shoot mechanism to extend the FOV with a correction procedure that allows calibration of the detector modules and correction for nonuniformities. We studied the effect of tracer uptake, background depth, detector CTR after validating the experimental data against the simulation setup.

A simulation study was performed to validate the experimental study. Furthermore, a simulation framework is useful because it allows easy exploration of a range of detector and geometry parameters, which can be difficult or even impossible to perform experimentally due to technical limitations. Moving forward, the simulation platform will be extended further to investigate iterative image reconstruction as well as a range of physical scanner parameters (e.g., TOF and DOI resolution, crystal depth and pitch, and phantom shape and size).

When comparing simulations and experiments, the images from simulations were more uniform and had less noise than the corresponding experimental images. As seen in table 1, this is manifested in the image quality metrics associated with noise (i.e., CNR and SNR), as can be expected since detector and electronic nonuniformities and noise do not contribute to the simulation. A second major difference between experiments and simulations was the detection sensitivity, or total number of counts registered with the same activity and geometry. In the simulations, there were 62% more singles counts. This discrepancy could have been caused by the combination of crystal pixels with less quality/sensitivity compared to the ideal LYSO model and the deadtime of the demo unit used in experiments. Deadtime itself can be caused by a very low triggering threshold to maintain maximum timing resolution or any bandwidth limitation for transferring the one-to-one coupled high count rate. The detailed information about internal structure of front-end ASIC and data flow, utilized in the demo unit, were proprietary and not shared with our group for further analysis.

For simplicity, we implemented simple 3D back projection with TOF information for image reconstruction. One additional reason for this is that iterative image reconstruction may not be straightforward to implement for fast image display with attenuation correction in the operating room. With a short effective acquisition time of \(60\) seconds and no iterative reconstruction algorithm, the image quality was limited, and with a 25 cm background depth, 6 mm spheres were only detectable when the 18:1 activity ratio was used (see figure 10). It is known that limited-angle PET can benefit from iterative reconstruction algorithms. While computationally intensive, GPU-based implementation of the image reconstruction may improve the image quality.

The uptake of \(^{18}\)F-FDG has been reported in several works as the maximum standardized uptake value (SUVmax), and values greater than 2.5 are usually considered malignancies [37, 38]. CRC values of 20%–30% for 10 mm spheres are reported for commercial TOF-PET scanners [39] with various activity concentrations including \(10 : 1\). Based on the wide range of uptake ratio values in clinical applications and development of more targeting tracers with higher uptake trace, while we experimented with 3 uptake ratios, we focused more on the 10:1 ratio as a mid-range value which is also used in NEMA-based scanner acceptance tests and quality assurance. The results presented here show that the uptake ratio has a significant effect on image quality and lesion detectability, and more specific radiotracers targeted to sentinel lymph nodes can expand the application of intraoperative PET imaging.
Furthermore, the results show that the effect of background, even with very low activity (high uptake ratio), prohibits the identification of small lesions ($< 6 \text{ mm}$) with a short scan time of $60 \text{s}$. Further investigation is required to show whether scatter correction methods can improve the image quality; however, the low statistics of the short acquisition time make this challenging. We intend to further investigate the effect of small crystal pixels and very good TOF-DOI resolution. This means that if small objects are desired with near real time image reconstruction, the acquisition time should be increased, which will also be the parameter that can be explored in simulations.

The data presented here showed that some of the artifacts caused by limited angle data could be reduced when using detectors with improved CTR. This is an active area of research by our group, among others, and we plan to implement improved detector technology with both improved DOI [40, 41] and CTR [42–44] in future work. Additionally, by using a 4.2 mm detector pixel pitch and no depth of interaction information, the detection of $< 4 \text{ mm}$ hot spheres with short acquisition is not practical. Despite the limited detector technology, limited detector coverage, and suboptimal image reconstruction technique, our results are encouraging in that by implementing improved TOF-PET technologies, one can aim at improved image quality, which may lead to an alternative solution to intraoperative imaging and ultimately improve the patient outcome.

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References

[1] J.E. Kalinyak, W.A. Berg, K. Schilling, K.S. Madsen, D. Narayanan and M. Tartar, Breast cancer detection using high-resolution breast PET compared to whole-body PET or PET/CT, Eur. J. Nucl. Med. Mol. Imaging 41 (2013) 260.

[2] P.J. Borgstein, R. Pipers, E.F. Comans, P.J. van Diest, R.P. Boom and S. Meijer, Sentinel lymph node biopsy in breast cancer: Guidelines and pitfalls of lymphoscintigraphy and gamma probe detection, J. Am. Coll. Surg. 186 (1998) 275.

[3] J. Alex, D. Weaver, J. Fairbank, B. Rankin and D. Krag, Gamma-probe-guided lymph node localization in malignant melanoma, Surg. Oncol. 2 (1993) 303.

[4] A.E. Giuliano, D.M. Kirgan, J.M. Guenther and D.L. Morton, Lymphatic mapping and sentinel lymphadenectomy for breast cancer, Ann. Surg. 220 (1994) 391.

[5] D. Krag, D. Weaver, J. Alex and J. Fairbank, Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe, Surg. Oncol. 2 (1993) 335.

[6] D.L. Morton, Technical details of intraoperative lymphatic mapping for early stage melanoma, Arch. Surg. 127 (1992) 392.

[7] S. Kaviani, N. Zeraatar, S. Sajedi, A. Akbarzadeh, N. Gorjizadeh, M.H. Farahani et al., Design and development of a dedicated portable gamma camera system for intra-operative imaging, Phys. Med. 32 (2016) 889.
[8] S. Kaviani, et al., Development and characterization of a compact hand-held gamma probe system, SURGEOGUIDE, based on NEMA NU3-2004 standards, 2016 JINST 11 P12004.

[9] E. Brogi, E. Torres-Matundan, L.K. Tan and H.S. Cody, The results of frozen section, touch preparation, and cytological smear are comparable for intraoperative examination of sentinel lymph nodes: A study in 133 breast cancer patients, Ann. Surg. Oncol. 12 (2005) 173.

[10] E.I. Johnston, R.A. Beach, S.M. Waldrop, D. Lawson and C. Cohen, Rapid intraoperative immunohistochemical evaluation of sentinel lymph nodes for metastatic breast carcinoma, Appl. Immunohistochem. Mol. Morphol. 14 (2006) 57.

[11] N.P. Alazraki, D. Eshima, L.A. Eshima, S.C. Herda, D.R. Murray, J.P. Vansant et al., Lymphoscintigraphy, the sentinel node concept, and the intraoperative gamma probe in melanoma, breast cancer, and other potential cancers, Sem. Nucl. Med. 27 (1997) 55.

[12] K. Dowlatshahi, M. Fan, H.C. Snider and F.A. Habib, Lymph node micrometastases from breast carcinoma, Cancer 80 (1997) 1188.

[13] K.L. Snook, G.T. Layer, P.A. Jackson, C.S. de Vries, S. Shousha, H.D. Sinnett et al., Multicentre evaluation of intraoperative molecular analysis of sentinel lymph nodes in breast carcinoma, Br. J. Surg. 98 (2010) 527.

[14] G.H. Lyman, A.E. Giuliano, M.R. Somerfield, A.B. Benson, D.C. Bodurka, H.J. Burstein et al., American society of clinical oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer, J. Clin. Oncol. 23 (2005) 7703.

[15] S. Pesek, T. Ashikaga, L.E. Krag and D. Krag, The false-negative rate of sentinel node biopsy in patients with breast cancer: A meta-analysis, World J. Surg. 36 (2012) 2239.

[16] S. Sajedi, L. Bläckberg, G. El Fakhri, H.S. Choi and H. Sabet, Intraoperative radio-guided imaging system for surgical applications, J. Nucl. Med. 60 (2019) 317.

[17] H. Sabet, B.C. Stack and V.V. Nagarkar, A hand-held, intra-operative positron imaging probe for surgical applications, IEEE Trans. Nucl. Sci. 62 (2015) 1927.

[18] F. Daghighian, J.C. Mazziotta, E.J. Hoffman, P. Shenderov, B. Eshaghian, S. Siegel et al., Intraoperative beta probe: A device for detecting tissue labeled with positron or electron emitting isotopes during surgery, Med. Phys. 21 (1994) 153.

[19] H. Sabet, H.B. Bhandari, H. Kudrolli, S.R. Miller and V.V. Nagarkar, A method for fabricating high spatial resolution scintillator arrays, IEEE Trans. Nucl. Sci. 60 (2013) 1000.

[20] H. Sabet, B.C. Stack and V.V. Nagarkar, A novel intra-operative positron imager for rapid localization of tumor margins, Proc. SPIE 9033 (2014) 90334K.

[21] S. Spadola et al., Design optimization and performances of an intraoperative positron imaging probe for radio-guided cancer surgery, 2016 JINST 11 P12019.

[22] J.C. Stendahl, Z. Liu, N.E. Boutagy, E. Nataneli, F. Daghighian and A.J. Sinusas, Prototype device for endoventricular beta-emitting radiotracer detection and molecularly-guided intervention, J. Nucl. Cardiol. (2020) in press.

[23] M.-A. Verdier, S. Spadola, L. Pinot, C. Esnault, Y. Charon, M.-A. Duval et al., Gamma-background rejection method for a dual scintillator positron probe dedicated to radio-guided surgery, Nucl. Instrum. Meth. A 912 (2018) 315.
[24] S.P. Povoski, I. Sarikaya, W.C. White, S.G. Marsh, N.C. Hall, G.H. Hinkle et al., Comprehensive evaluation of occupational radiation exposure to intraoperative and perioperative personnel from 18f-FDG radioguided surgical procedures, *Eur. J. Nucl. Med. Mol. Imaging* **35** (2008) 2026.

[25] J.W. Cates and C.S. Levin, Evaluation of a clinical TOF-PET detector design that achieves ≤100 ps coincidence time resolution, *Phys. Med. Biol.* **63** (2018) 115011.

[26] S. Surti and J.S. Karp, Design considerations for a limited angle, dedicated breast, TOF PET scanner, *Phys. Med. Biol.* **53** (2008) 2911.

[27] S. Sajedi, L. Blackberg, G.E. Fakhri and H. Sabet, Limited-angle TOF-PET for intraoperative surgical applications: latest results, in proceedings of 2020 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), Boston, MA, U.S.A., 31 October–7 November 2020, pp. 1–3.

[28] C. Bluemel, A. Schnelzer, A. Okur, A. Ehlerding, S. Paepke, K. Scheidhauer et al., Freehand SPECT for image-guided sentinel lymph node biopsy in breast cancer, *Eur. J. Nucl. Med. Mol. Imaging* **40** (2013) 1656.

[29] J. Jiang, K. Li, Q. Wang, K. Puterbaugh, J.W. Young, S.B. Siegel et al., A second-generation virtual-pinhole PET device for enhancing contrast recovery and improving lesion detectability of a whole-body PET/CT scanner, *Med. Phys.* **46** (2019) 4165.

[30] J. Jiang, S. Samanta, K. Li, S.B. Siegel, R.A. Mintzer, S. Cho et al., Augmented whole-body scanning via magnifying PET, *IEEE Trans. Med. Imaging* **39** (2020) 3268.

[31] S. Sajedi, L. Blackberg, B. Vittum, A. Devabhaktuni, M.M. Nejad, G.E. Fakhri et al., Limited-angle TOF-PET for intraoperative surgical application, in proceedings of 2019 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), Manchester, U.K., 26 October–2 November 2019, pp. 1–4.

[32] A.L. Goertzen and D.V. Elburg, Performance characterization of MPPC modules for TOF-PET applications, *IEEE Trans. Radiat. Plasma Med. Sci.* **3** (2019) 475.

[33] A. Stolin, G. Jaliparthi, R.R. Rayman, J. Brefczynski-Lewis, S. Majewski, J. Qi et al., Evaluation of hamamatsu PET imaging modules for dedicated TOF-capable scanners, *IEEE Trans. Radiat. Plasma Med. Sci.* **3** (2019) 634.

[34] E. Yoshida, H. Tashima, G. Akamatsu, Y. Iwao, M. Takahashi, T. Yamashita et al., 245ps-TOF brain-dedicated PET prototype with a hemispherical detector arrangement, *Phys. Med. Biol.* **65** (2020) 145008.

[35] Performance measurements of positron emission tomographs NU 2-2007, in *NEMA Standards Publication*, National Electrical Manufacturers Association, Rosslyn, VA, U.S.A. (2007).

[36] S. Sajedi, N. Zeraatkar, M. Taheri, S. Kaviani, H. Khammohammadi, S. Sarkar et al., Development and preliminary results of xtrim-PET, a modular cost-effective preclinical scanner, *Nucl. Instrum. Meth. A* **940** (2019) 288.

[37] D. Fuster, J. Duch, P. Paredes, M. Velasco, M. Muñoz, G. Santamaría et al., Preoperative staging of large primary breast cancer with [18f]fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures, *J. Clin. Oncol.* **26** (2008) 4746.

[38] T.S. Aukema, M.E. Straver, M.-J.T.V. Peeters, N.S. Russell, K.G. Gilhuijs, W.V. Vogel et al., Detection of extra-axillary lymph node involvement with FDG PET/CT in patients with stage II–III breast cancer, *Eur. J. Cancer* **46** (2010) 3205.
[39] S. Surti et al., Performance of Philips Gemini TF PET/CT scanner with special consideration for its time-of-flight imaging capabilities, J. Nucl. Med. 48 (2007) 471.

[40] L. Bläckberg, G.E. Fakhri and H. Sabet, Simulation study of light transport in laser-processed LYSO:Ce detectors with single-side readout, Phys. Med. Biol. 62 (2017) 8419.

[41] L. Blackberg, M. Moebius, G.E. Fakhri, E. Mazur and H. Sabet, Light spread manipulation in scintillators using laser induced optical barriers, IEEE Trans. Nucl. Sci. 65 (2018) 2208.

[42] L. Blackberg et al., Novel staggered scintillator configurations for brain TOF-DOI PET detector, J. Nucl. Med. 61 (2020) 386.

[43] W.A. Worstell, S. Sajedi, L. Blackberg, Y. Feng, M.J. Aviles, S. Butler et al., Measurement of the parametrized single-photon response function of a large area picosecond photodetector for time-of-flight PET applications, IEEE Trans. Radiat. Plasma Med. Sci. 5 (2021) 651.

[44] L. Bläckberg, S. Sajedi, G.E. Fakhri and H. Sabet, A layered single-side readout depth of interaction time-of-flight-PET detector, Phys. Med. Biol. 66 (2021) 045025.