Photo-Guided Sentinel Node Mapping in Breast Cancer Using Marker-Free Photo-Gamma Fusion Lymphoscintigraphy

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Abstract

Purpose Photo-gamma fusion lymphoscintigraphy (PGFLS) was developed by overlying a conventional planar gamma image on a photograph for the guidance of sentinel node biopsy. The feasibility and accuracy of PGFLS was assessed in breast cancer patients.

Methods A digital camera and a gamma camera were coordinated to obtain photograph and gamma images from the same angle. Using the distance to the object and calibration acquisition with a flat phantom and radioactive markers, PGFLS was performed both in phantom and in patients without fiducial markers. Marker-free PGFLS was verified using flat phantom, anthropomorphic phantom with markers simulating sentinel nodes and breast cancer patients. In addition, the depth of the radio-

active marker or sentinel node was calculated using two gamma images taken at right angles. The feasibility and accuracy of PGFLS were assessed in terms of mismatch errors of co-registration and depth with reference to the data from SPECT/CT.

Results The mismatch error was less than 6 mm in the flat phantom image at a distance from 50 to 62 cm without misalignment. In the anthropomorphic phantom study, co-registration error was 0.42 ± 0.29 cm; depth error was 0.51 ± 0.37 cm, which was well correlated with the reference value on SPECT/CT (x scale: $R^2=0.99$, $p<0.01$; y scale: $R^2=0.99$, $p<0.01$; depth: $R^2=0.99$, $p<0.01$). In ten patients with breast cancer referred for lympho-SPECT/CT, PGFLS enabled photo-guided sentinel lymph node mapping with acceptable accuracy (co-registration error, 0.47 ± 0.24 cm; depth error, 1.20 ± 0.41 cm). The results from PGFLS showed close correlation with those from SPECT/CT (x scale: $R^2=0.99$, $p<0.01$; y scale: $R^2=0.98$, $p<0.01$; depth: $R^2=0.77$, $p<0.01$).

Conclusions The novel and convenient PGFLS technique is clinically feasible, showing acceptable accuracy and providing additional visual and quantitative information for sentinel lymph node mapping. This approach will facilitate photo-guided sentinel lymph node dissection in breast cancer.

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Introduction

Axillary node status is a major prognostic factor in early-stage breast cancer. However, routine axillary lymph node dissection is associated with increased risk of lymphedema,

chronic pain, and paresthesia. Sentinel lymph node biopsy (SNB) can reduce these complications substantially and is now accepted as part of the standard routine care in patients with breast cancer [1–3].

The accuracy and the identification rate of SNB depend on its technical aspects and the surgeon's experience. In a study that included 30 SNBs, surgeons achieved a 90 % rate of sentinel lymph node (SLN) identification with a false-negative rate of less than 5 % [4]. The accuracy of SNB is increased and the invasiveness of the procedure is reduced by providing the surgeon with a visual map of the sentinel nodes. Lymphoscintigraphy has the potential to improve accuracy and reduce morbidity compared to gamma probing alone [5, 6]. The combination of radiolabeled colloid, lymphoscintigraphy, and blue dye can increase success rates and reduce false-negative rates [4]. Although lymphoscintigraphy identifies atypical drainage patterns and directs the surgeon to the site of the sentinel node, it provides limited spatial information. In particular, this technique lacks the ability to disclose the three-dimensional location or depth of the node and the relationship between the neighboring structures.

Since its introduction, hybrid SPECT/CT scan has been known as the most reliable imaging technique to show the exact location of sentinel lymph nodes [7]. It is a sensitive method for the detection of sentinel lymph nodes, in addition to providing specific anatomical information. However, it is associated with additional radiation exposure from the CT and long acquisition time, which is incompatible with everyday routine use, and it is more expensive than the planar scan, which is cost effective, fast, and appears to be more appropriate for daily routine practice.

The fundamental information provided by SPECT/CT is the localization and depth of sentinel lymph nodes in the surgical field. Because surgeons depend primarily on visual information during an operation, the most desirable method to convey this information is via a photograph or video of the operation field. Planar lymphoscintigraphy can be merged and displayed on the photograph or video of the operation field, providing the surgeon with a map of sentinel nodes. Additional orthogonal scans can reveal the depth of the sentinel node. The development of photo-gamma fusion could therefore provide a fast, safe, cheap and intuitive alternative to SPECT/CT for sentinel lymph node guidance. However, this technique currently requires using visible and radioactive fiducial markers and considering the distance between the patient and camera on every image acquisition [8, 9].

We devised a convenient method of photo-gamma fusion for sentinel lymphoscintigraphy that does not require the use of fiducial markers on every acquisition and is capable of compensating for the distance from the camera. The aim of the present study was to verify the feasibility, accuracy, and clinical efficacy of this method for sentinel lymph node biopsy in breast cancer patients.

Materials and Methods

Marker-Free Photo-Gamma Fusion Lymphoscintigraphy (PGFLS)

All gamma images for sentinel lymph node lymphoscintigraphy were obtained with a dual head gamma camera with CT (Millennium VG Hawkeye SPECT/CT, GEMS, Milwaukee, WI). A 10 megapixel digital camera (Allinfolk ALC-M1000) was installed on the lateral border of the gamma camera gantry. The distance between the digital camera and the center of the gamma camera was 50.6 cm (Fig. 1). The digital camera could be tilted by moving the head of the gamma camera. The digital camera was connected with a USB cable, and the photographs were taken remotely using vendor-provided software. The photographs were written onto the hard drive in a JPEG format as 1,600×1,200 pixel matrix with unsigned 24-bit integers.

For planar and SPECT images, 37 MBq/0.5 ml of ^{99m}Tc -human serum albumin for clinical imaging and 3.7 MBq/0.1 ml of ^{99m}Tc -pertechnate were used for validation phantom images. Planar images were acquired and stored as a 256×256 matrix with unsigned 16-bit integers in the DICOM format on the PACS system. Images were converted to a JPEG format as 1,024×1,024 matrices with unsigned 24-bit integers. SPECT images were obtained with a low-energy parallel collimator (159 KeV±10 %) and the step and shoot method (40 s per scan, 60 scans per 360°, 64×64 matrix). CT was performed using X rays with 145 KV, 2.5 mA (2.6 RPM, 360°, 256×256 matrix).

The field of view of a camera varies with the distance between the object and the camera. Image distortion, such as perspective distortion, can occur in a photograph, whereas the gamma image taken through a parallel collimator does not suffer from perspective distortion. Therefore, fixed co-registration of a photograph and gamma image is not possible at variable distances from the object. Instead, we calculated the transformation matrix and co-registered both images at a given distance as reference setting. If the image was taken at a distance farther than the reference distance, the gamma image was reduced proportionally and both were co-registered. Although the photograph could be transformed, the transformed photograph did not appear realistic and we therefore changed the gamma image. Once the reference transformation matrix had been set up according to the algorithm, using the three fiducial markers and the distance between the object and the digital camera, we co-registered the photograph and gamma images without fiducial markers. The distance could be easily measured using a laser distance meter (DISTO D3a BT, Leica Geosystems AG, Switzerland).

We prepared a calibration phantom, namely a board with several radioactive markers in a radial pattern. The custom-

Fig. 1 Marker-free photo-gamma fusion lymphoscintigraphy (PGFLS) procedure. **a** A digital camera was attached to the gantry of the gamma camera. The gamma scan and photograph were taken on a flat board with radioactive markers. **b** The transformation matrix was calculated using the gamma image and photograph, which were taken at the reference distance (50 cm). **c** If the distance is changed, the gamma image is modified accordingly to conform to the new distance.

Photographs and modified gamma images were co-registered and merged using a pre-calculated transformation matrix. **d** Fusion image at the reference distance. All radioactive markers (three reference markers and other non-reference markers) were well matched up on the PGFLS images. The mismatch error was minimal. **e** Fusion image at 12 cm from reference distance (62 cm). PGFLS also showed good registration quality

made markers contained approximately 185 KBq of ^{99m}Tc -pertechnetate. We set 50 cm as the reference distance between the phantom and the digital camera. A transformation matrix of the reference setting was obtained (calibration step) using the three markers, which were aligned evenly 20 cm off the center of the phantom (Fig. 1). The accuracy or mismatch errors of our method, which are described in the following sections, were assessed using other markers.

All photographs and planar gamma images were co-registered using an affine transformation algorithm. The co-registration method used was similar to a previously published method [10]. The affine transformation and other image conversions were performed with open-source program suites (ImageMagick image toolkit). Transformed images were fused using multiply methods implemented in the ImageMagick toolkit. All steps for image manipulation were automated with open source scripting language (AutoIT).

– Measurement of expected mismatch error

Because the accuracy of our fusion method depends on the distance and angle between the reference setting and measuring setting, we measured the mismatch error at different distances and angles. We measured mismatch errors in terms of the distance from the center of the phantom, displacement from the reference

distance (50 cm), and varying angle (Fig. 1). The mismatch errors between the photograph and the gamma image were expressed as mean and standard deviation in mm.

– Calculation of the depth of the hot spot on the PGFLS image

Generally, the depth of the hot spot cannot be measured in a two-dimensional planar image without a three-dimensional image such as that provided by tomography. However, if the region of interest is definite and easy to recognize, the depth of the hot spot can be measured by obtaining a perpendicular additional two-dimensional image alternative to three-dimensional tomography. We measured the distance between the overlying skin (object) and the camera, and used the perpendicular gamma scan to calculate the distance between the region (hot spot) and the center, which enabled the calculation of the depth of the hot spot.

PGFLS Using an Anthropomorphic Phantom

The overall robustness of PGFLS was assessed with an anthropomorphic torso phantom. Radioactive markers

Fig. 2 Photo-gamma fusion lymphoscintigraphy (PGFLS) using an anthropomorphic phantom. **a** Photo-gamma fusion lymphoscintigraphy and SPECT/CT were obtained using an anthropomorphic phantom. A surface-rendering image was generated from the SPECT/CT and compared with the fusion image. The position of the hot spot on PGFLS was accurately co-registered on the surface-rendering SPECT/CT image. The mismatch error of location between PGFLS and SPECT/CT was minimal. **b** The depth of the hot spot was measured on SPECT/CT. **c** The depth by PGFLS was closely correlated to the depth by SPECT/CT

simulating hot sentinel lymph nodes were placed in the interior of the phantom, approximately 1–10 cm beneath the axillary surface. In addition, the grid-shaped markers were attached to the surface of the phantom, which was visualized using the photograph and CT image. We performed PGFLS at an angle of 45°. The axillary oblique photo-gamma fusion images and the depths of the markers were obtained as described previously.

SPECT/CT scans were performed using the same settings. Surface-rendering images were produced from CT images of the SPECT/CT scans and the position of the markers was projected on these images with a 45° angle (Osirix medical imaging software, The Osirix Foundation, Geneva, Switzerland). In addition, the depth of the markers, i.e. the distance between the marker and the overlying skin, was measured at a 45° angle from the CT images.

The PGFLS image was compared with the surface-rendering SPECT/CT. The locations of radioactive markers were measured using the x and y axes of the grid to calculate the mismatch error. Using these x and y scales, the mismatch difference between PGFLS and SPECT/CT were measured (Fig. 2).

PGFLS of the Patients with Breast Cancer

A total of ten women (age, 40.2 ± 7.6 years) who were referred for sentinel lympho-SPECT/CT between April 1st and April 30th, 2012, were consecutively enrolled. The patients were diagnosed with biopsy-proven

clinically node-negative breast cancer (cTis, 1–3, cN0, M0). For image acquisition, the patient was positioned with her arm raised. A reference grid was attached and fixed with polyurethane film dressing (Tegaderm, 3 M) on the axillary area. The grid was positioned inside the space bordered by the latissimus dorsi muscle, pectoralis muscle, arm-axilla fold, and the breast. For lymphatic mapping, ten patients received a ^{99m}Tc -human serum albumin injection of approximately 0.2 ml at the periareolar area (7.4–14.8 MBq).

Our routine procedure for sentinel lymph node SPECT/CT consists of a conventional planar imaging step and a SPECT/CT acquisition step. In addition, a photograph was taken for fusion lymphoscintigraphy. In all patients, dynamic planar lymphoscintigraphy was performed for 3 min immediately after injection (anterior view). An oblique image anterior to the axillary area and another image perpendicular to the oblique axillary image were taken for 2 min. The oblique image was scanned for the breast and axillary area at the angle of 45°. Lympho-SPECT/CT was then performed.

Photo-gamma fusion and depth measurements were performed as previously described. We obtained a sentinel lymph node marked surface-rendering image and measured the depth from the SPECT/CT image. The fusion images and depth were compared with those of SPECT/CT, using the method described previously (Fig. 3).

Before performing the sentinel lymph node mapping and biopsy in the operation room, the hot spot for the sentinel

Fig. 3 Photo-gamma fusion lymphoscintigraphy (PGFLS) in a patient. **a** A 47-year-old woman underwent PGFLS and sentinel-SPECT/CT. **b** On the tomographic images, the sentinel node could be visualized clearly. **c, d** A photo-gamma fusion image and surface-rendering images were produced, and they showed a good co-registration result.

The mismatch error between the 2 images was 0.18 cm. The depth by PGFLS was 1.7 cm and the depth by SPECT/CT was 2.8 cm. **e** The depths by PGFLS and SPECT/CT were plotted for ten patients, and showed moderate correlation

lymph node on the axilla was marked using a gamma probe. The patients underwent sentinel lymph node mapping and biopsy following the institution's routine protocol.

Statistical Analyses

All data were expressed as mean $\pm$ standard deviation. The correlation between the data from PGFLS and those from SPECT/CT was evaluated using the Pearson correlation coefficient. All statistical analyses were performed using Medcalc software (MedCalc Software version 11.4.4, Mariakerke, Belgium). A P value of < 0.05 was considered statistically significant.

Results

Technical Feasibility and Accuracy of PGFLS

PGFLS could be performed without difficulty and was technically feasible. The co-registration results for all PGFLS images were accurate at various distances using a flat reference phantom. A calibration was performed at the reference distance of 50 cm to obtain the transformation matrix for the gamma camera and digital camera. After that, the distance was only modified before performing the lymphoscintigraphy and taking the photograph.

Table 1 Mismatch errors on marker-free photo-gamma fusion lymphoscintigraphy at various distances between the camera and the phantom

Distance between photo camera and the object (phantom)	Displacement from the center of the reference triangle (cm)					Mean (SD)
	Center (0 cm)	5 cm off	10 cm off	15 cm off	20 cm off (reference)	
Reference (50 cm)	0.22	0.17	0.21	0.20	0.13	0.19 (0.04)
+3 cm (53 cm)	0.12	0.21	0.30	0.33	0.28	0.25 (0.08)
+6 cm (56 cm)	0.08	0.30	0.33	0.38	0.38	0.29 (0.12)
+9 cm (59 cm)	0.22	0.43	0.45	0.46	0.45	0.40 (0.10)
+12 cm (62 cm)	0.28	0.48	0.53	0.59	0.58	0.49 (0.13)
Mean (SD)	0.18 (0.08)	0.32 (0.13)	0.36 (0.13)	0.39 (0.15)	0.36 (0.17)	0.32 (0.14)

SD standard deviation

At the reference distance of 50 cm, all radioactive markers (three reference markers and other non-reference markers) were well matched up on the PGFLS images (Fig. 1d). The mismatch error was less than 0.22 cm (Table 1), which was clinically acceptable, considering the spatial resolution of our gamma camera system (radial and central spatial resolution <0.99 cm) and the pixel size of our lymphoscintigraphy (0.47 cm/pixel).

At the distances of 53, 56, 59, and 62 cm, PGFLS showed good registration quality (Table 1, Fig. 1e). There was a trend towards an increase in mismatch error with distance. However, the average error was only 0.32 ± 0.14 cm (range, 0.08–0.59), and less than 1 pixel in width up to a distance of 62 cm. The error measurement tended to be lower towards the center of the object.

Unlike distance, which can be compensated for during the fusion process, the angle difference between the calibrating and measuring settings had a significant effect on the accuracy of the results. Measurements were taken at 15°, 30°, and 45° angles of misalignment with respect to the calibration setting, which increased mismatch error to 40.8, 61.0, and 79.0 pixels (0.0516 cm/pixel) using markers positioned 20 cm off the center. Greater distances from the marker were associated with higher mismatch error with respect to the angle deviation (data not shown).

Verification of PGFLS Using an Anthropomorphic Phantom

We used a three-dimensional anthropomorphic phantom to simulate sentinel lymph node placement in the axillary area, and included 14 radioactive markers at various depths (range, 1.26–9.21 cm) beneath the axilla. Using PGFLS, the fusion image and depth of each marker (sentinel node) were successfully obtained.

The positions of the hot spots on PGFLS were accurately co-registered on surface-rendering SPECT/CT images. The location mismatch error between PGFLS and SPECT/CT was 0.42 ± 0.29 cm (Table 2), comparable to that of the flat phantom image (0.32 cm). The x and y scales of the markers on PGFLS and on SPECT/CT were closely correlated (x scale: $R^2=0.99$, $p<0.01$; y scale: $R^2=0.99$, $p<0.01$).

The depths of the hot spots on PGFLS were closely correlated with those of SPECT/CT, which was assumed as the gold standard ($R^2=0.99$, $p<0.01$) (Fig. 2c). The mismatch for the depth measurement was 0.51 ± 0.37 cm (Table 2). The depth measurement by SPECT/CT was greater than that obtained by PGFLS (0.49 vs. 0.44 cm, $p<0.01$).

Verification of PGFLS in Patients Who Underwent Clinical Sentinel SPECT/CT

Our method could be applied in ten patients without difficulties, in comparison with conventional lymphoscintigraphy.

Table 2 The errors of depth and mismatch from marker-free photo-gamma fusion lymphoscintigraphy (PGFLS)

Markers	Depth by SPECT/CT (cm)	Depth by PGFSL (cm)	Depth error (cm)	Mismatch error (cm)
No. 1	1.26	0.24	1.02	0.17
No. 2	2.40	1.44	0.96	0.28
No. 3	2.71	1.97	0.74	0.58
No. 4	3.28	2.82	0.46	0.14
No. 5	4.24	3.45	0.79	0.83
No. 6	4.49	4.32	0.17	0.07
No. 7	4.64	4.30	0.34	0.42
No. 8	4.88	4.33	0.55	0.81
No. 9	5.19	4.21	0.98	0.46
No. 10	6.43	6.42	0.01	0.62
No. 11	6.70	5.85	0.85	0.91
No. 12	6.73	6.65	0.08	0.29
No. 13	7.03	6.91	0.12	0.04
No. 14	9.21	9.11	0.10	0.25
Mean (SD)			0.51 (0.37)	0.42 (0.29)

SD standard deviation; PGFSL photo-gamma fusion lymphoscintigraphy

The procedure time for PGFLS was less than 15 min, whereas that of SPECT/CT was 35 min. The sentinel node uptakes were discernible on planar scan and SPECT/CT for all patients.

PGFLS could successfully depict SLNs on the photograph. A representative result is shown in Fig. 3. The co-registration was accurate, showing a mismatch error of 0.47 ± 0.24 cm, which was comparable to that of the anthropomorphic phantom (0.42 cm). The x and y scales of the sentinel node on PGFLS and on SPECT/CT were closely correlated (x scale: $R^2=0.99$, $p<0.01$; y scale: $R^2=0.98$, $p<0.01$).

The depth of the sentinel node by PGFLS was also closely correlated with that obtained by SPECT/CT ($R^2=0.77$, $p<0.01$) (Fig. 3e). The depth by SPECT/CT was slightly greater than that measured by PGFLS (2.3 ± 0.82 vs. 1.1 ± 0.57 cm, $p<0.01$), with a difference of 1.20 ± 0.41 cm. Although the error in the depth measurement was small, it was twice as large as that obtained with the anthropomorphic phantom.

Discussion

Clinical Indications for Sentinel Lymph Node Imaging and Biopsy

The combination of preoperative lymphoscintigraphy with intra-operative exploration with a gamma probe provides useful information for sentinel lymph node biopsy in breast

cancer. However, lymphoscintigraphy and the auditory signal from the probe lack spatial and navigational information [11], and the success of the procedure therefore depends on the experience and anatomical knowledge of the surgeons. Lymphoscintigraphy only provides a rough contour of a patient's body. Therefore, correlation of the surgical field with the lymphoscintigraphy data is difficult for novice surgeons, particularly in cases of unexpected node drainage, deep-seated nodes and atypical anatomy of neighboring tissues. Lymphoscintigraphy and the gamma probe do not provide information on the depth of the sentinel lymph node, and only show the direction of its placement [12]. Lymphoscintigraphy can roughly estimate the depth with an additional orthogonal scan. Sentinel nodes can be located close to the surface or at a distance from the skin, and deeper sentinel nodes make it difficult to perform non-invasive procedures. Advance knowledge of the depth of the sentinel node would enable the surgeon to avoid unnecessary tissue destruction during the operation.

SPECT/CT can provide information on the anatomical context and the depth of the sentinel lymph node more clearly through its tomographic representation [13]. It can find sentinel nodes with weak uptake and detect nodes residing in the vicinity of an injection site, as well as overlaps. Surgeons can correlate the information from the SPECT/CT with the surgical field. Although SPECT/CT provides a tomographic image and bears three-dimensional information, it is different from the surgeons' visual perspective and is not natural or intuitive in all cases. The simplest and most natural way to convey the information of the sentinel lymph node is to display it on the surgical field itself. The overlay of medical information on the video of the patient's body has been attempted [14]. MR images were overlaid on the surface of the brain during surgery. These studies indicate that surgeons prefer to see the lesion with their own eyes. Marking the sentinel node on the surface-rendered CT image from SPECT/CT provides a perspective that is similar to that of the surgeon's view, but lacks information about skin texture and landmarks. Meanwhile, a simple overlay display method cannot express stereopsis, and the depth of the sentinel lymph node can therefore not be assessed on an overlay image. One solution to this problem would be to present the depth measurement from the skin with image.

Accuracy of PGFLS

The gamma scan provides functional information and high contrast between the lesion and background. However, it cannot accurately convey the contextual information with respect to the neighboring anatomical structures, which is essential for surgical procedures. The PGFLS method provides information on the location and depth of the sentinel

node in a convenient way, without compromising intra-operative radio-guided power. PGFLS can overcome the problems associated with scintigraphy and help surgeons with surgical planning and identification of radioactive sentinel lymph nodes.

Previous efforts to combine planar gamma images with a photograph of the patient's body have been made. Previously suggested methods assumed that the surface of the object is flat and the distance between the object and the camera is not under consideration. Nanji et al. designed the method of planar visual fusion scintigraphy using fiducial markers on every imaging time for image registration [15]. Unlike our method, they did not consider the actual distance between the object and the camera, which could lead inaccurate results, especially when the photograph is taken close to the patient.

We measured the distance every time, and revised the transformation matrix on the basis of the information obtained. This leaves the fiducial marker, while maintaining a high level of co-registration accuracy. In previous studies, the optical camera was fixed on the ceiling directly above the gamma camera to allow the estimation of the thickness/depth of the object. Because the gamma and optical cameras were fixed in one position, the calibration did not need to be repeated. This fixed location of cameras makes fiducial markers unnecessary and the settings are simple. However, the axillary area in which the SLNs are located is tilted at an approximately 45° angle, and the image cannot be obtained from the surgeon's perspective when the camera is fixed on the ceiling. Therefore, the camera should be attached to the rotating gantry or head of the SPECT/CT to adjust its angle, and the distance between the camera and the axillary area needs to be measured for image registration.

Haneishi et al. suggested a fusion method using a three-dimensional image of the operation field, obtained by an optical camera obliquely attached to the mini gamma camera in an operating room [16]. We measured the distance between the camera and the axillary surface to adjust the transformation matrix. These efforts would serve to overcome the perspective error of the optical camera lens in an uneven operation field close to the camera.

PGFLS was accurate enough and safe for routine application in the clinic. It is not an invasive procedure and does not involve additional radiation exposure from CT. Mismatch errors of location were small and all similar with respect to the flat phantom, three-dimensional phantom, and breast cancer patients, and were small for all measurements regardless of the depth or distance values. The mismatch error of our method was only 0.47 ± 0.24 cm according to patients' data, which is acceptable, considering that the spatial resolution of common commercial gamma cameras is around 1 cm. Our results indicate that PGFLS is accurate enough for clinical application without fiducial

markers if it is calibrated once before the inclusion of the patient.

Depth measurements by PGFLS were not entirely accurate, showing a greater mismatch error than that obtained by phantom images. Nevertheless, the depth by PGFLS was closely correlated to that of SPECT/CT. The depth obtained by PGFLS tended to be smaller than that measured by SPECT/CT. The exact reason for this difference is not clear, but the poor spatial resolution of orthogonal scintigraphy and technical error might have played a role.

The angle of camera had a significant effect on the accuracy of PGFLS, suggesting that if PGFLS is performed out of alignment, it should be considered incorrect, as there was no compensatory mechanism for angle deviation in our PGFLS method.

PGFLS has higher throughput than SPECT/CT and is less time-consuming. In general, acquiring SPECT/CT images takes longer than generating a planar gamma image. The acquisition of planar gamma images for PGFLS does not involve an additional time period, unlike SPECT. In addition, PGFLS does not require the placement of fiducial markers, which is an annoying interruption for patients and technicians, and this improves throughput rates. It does not interfere with pre-established radiotracer-based lymphoscintigraphy. Fiducial markers can sometimes hide or hinder true radiotracer accumulation, underscoring the need to develop a marker-free fusion method.

PGFLS is easy to perform and inexpensive, requiring only an optical digital camera of general purpose and a ruler for measuring distances.

Other Application of PGFLS

Because humans depend mostly on visual information, optical image-guided approaches should have several applications besides sentinel node mapping. PGFLS could be applied to other nuclear imaging methods, such as radioiodine and bone scans [17]. Lesions identified on a nuclear image could be objectively localized using this technique. An unusual accumulation of radiotracer could be co-registered with other imaging modalities, or evaluated in the clinic through physical examination with the photo- gamma fusion method.

Photo-guided gamma fusion could be useful to guide the biopsy to the site of hot uptake on the gamma image. For example, sites showing unusual accumulation of applied radioiodine could be targeted and biopsied with the guidance of ultrasonography and the photo-guided approach. The unique information on the depth of the lesion provided by our method could be of significant value for the safety and effectiveness of this type of procedure. Although SPECT/CT has been shown to be a useful method, physicians performing ultrasonography were not always able to correlate sonographic findings with tomographic information.

Photograph fusion technique can be potentially linked to all types of medical imaging modalities including planar images, such as those obtained by scintigraphy or radiography, and tomographic images, such as those of SPECT/CT, PET, and CT.

Limitations of PGFLS

Our method has some limitations. First, the spatial resolution of the gamma image and the photograph differ from each other. The spatial resolution of the gamma image is low in comparison to that of the photograph, which can generate inaccurate results. Nevertheless, the mismatch error in our study was within acceptable levels.

Second, the process of measuring the distance and installing the digital camera could be associated with technical inaccuracy. The calculated depths from PGFLS were approximately 1 cm shorter than the measured depths from SPECT/CT, although there was good correlation between them. We calculated the depth of the sentinel node by subtracting the manually measured distance between the gamma camera and the patient's axillary surface from the calculated distance between the gamma camera and the sentinel node. During the manually measuring process, the potential misalignment could introduce error in the measurement of the node depth. The optical characteristics of the digital camera can also cause inaccurate measurements. If the camera is customized to have ability to measure the distance from the camera automatically as well as to take a photograph, it could improve the technical accuracy of the results.

Third, our method lacks three-dimensional information. If PGFLS could represent depth, it would be more realistic and natural for surgeons.

An important technical problem is related to the profound differences in the underlying mechanism between optical and gamma imaging. The use of a lens in optical imaging causes a perspective effect by which the size of the object is perceived differently according to the distance, in contrast to gamma imaging with a parallel collimator. From this perspective, it is impossible to co-register all points on both images unless the object is flat and the distance is fixed. Time-of-flight camera, recently developed, or stereo camera, can measure the distance of each pixel in the photo and depict the object three-dimensionally. The stereo-photograph might help to partially remove a perspective effect from general photograph. However, their costs are high and implementation complex. Therefore, they did not seem practical. However, the co-registration error with general photograph appeared to be acceptable by applying the height variable. Restricting the field of view, for example to the inner points rather than the registration points, results in more precise co-registration.

PGFLS is a promising method, and additional studies on its clinical efficacy, such as its effect on reducing operation

time and the learning curve for novice surgeons, are warranted. Wider applications are expected with the other modalities except lymphoscintigraphy.

Conclusion

We demonstrated that the novel PGFLS method is clinically feasible and shows acceptable accuracy, providing additional visual and quantitative information for sentinel lymph node mapping. This approach will enable image-guided sentinel lymph node dissection in breast cancer.

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Conflict of Interest All authors declare that they have no conflict of interest.

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