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著者	市原 裕紀
著者別表示	Ichihara Hironori
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Evaluation of the subtraction method utilizing posterior view for improving visibility of the sentinel lymph nodes for lymphoscintigraphy in breast cancer

Hironori Ichihara (MS)¹⁾²⁾, Masahisa Onoguchi (PhD)²⁾, Akihiro Kikuchi (PhD)³⁾,
Takayuki Shibutani (MS)²⁾

1) Division of Nuclear Medicine, Chiba Cancer Center, Chiba, Japan

2) Department of Quantum Medical Technology, Graduate School of Medical Sciences,
Kanazawa University, Ishikawa, Japan

3) Department of Radiological Technology, Faculty of Health Science, Hokkaido
University of Science, Hokkaido, Japan

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Abstract

Objective: This study aimed to evaluate the usefulness of the subtraction method for improving sentinel lymph node (SLN) visibility by reducing scattering near the injection site.

Methods: Images of two phantoms for the injection site and SLNs built using an original design were simultaneously acquired using a dual-head camera equipped with a low-energy high-resolution (LEHR) on the lower detector (posterior view) and a low-energy general-purpose (LEGP) collimator on the upper detector (anterior view). Subtraction method images were created by subtracting the posterior view from the anterior view, the latter of which was designated as the conventional method. Image contrast was calculated from the counts of regions of interest (ROI) placed on the two phantoms of the injection site and SLNs. SLNs visibility to a distance from the injection site and a radioactivity ratio based on the injection site (15 MBq) was evaluated by image contrast and visual interpretation.

Results: The best improvement in contrast occurred at a distance of 20 pixels (1.08 mm/pixel) from the injection site, and improved further as the lymph node radioactivity is smaller. The SLNs visibility corresponding to a distance of 20 pixels improved significantly ($p < 0.001$), from 1/2560 of radioactivity at the injection site (approximately 6 kBq) to 1/640 (approximately 23 kBq), and SLN was only detectable using the subtraction method. SLN (1/5120, approximately 3 kBq) was difficult to detect even with the subtraction method, whereas SLN with a ratio $\geq 1/320$ (approximately 46 kBq) was easily detected even with the conventional method. These visibilities did not differ significantly between the two methods ($p = 0.16$ and >0.32 , respectively). The subtraction method could detect SLNs near the tumor on clinical images.

Conclusions: The subtraction method improved SLN visibility near the injection site by reducing scattering from the injection site. Furthermore, an advantage of the subtraction method is that it does not require additional imaging because the posterior view is obtained simultaneously and utilized.

Key word: Sentinel lymph node, Lymphoscintigraphy, Breast cancer

INTRODUCTION

The presence of cancer cells in the sentinel lymph node (SLN) is an important factor used in cancer staging [1]. Most facilities use preoperative lymphoscintigraphy to localize SLNs in patients with breast cancer. In breast cancer cases, lymphoscintigraphy reveals drainage from the tumor to axillary lymph nodes and accurately localizes SLNs within the body, thus providing surgical assistance [2-6]. Currently, lymphoscintigraphy is the standard means of evaluating SLNs from tumors.

There are some disadvantages to lymphoscintigraphy. For example, a large amount of radioactivity is retained at the injection site; however, the target SLN is small in size and retains only a small amount of radioactivity [4]. Therefore, radioactive scattering may cover SLNs near the injection site on images.

To address this disadvantage, multiple methods [7-18] have been developed to minimize the effects of scattering and to improve SLN visibility during lymphoscintigraphy imaging. However, the use of these methods requires a new imaging in addition to as the usual imaging.

We devised a subtraction method that utilizes a posterior view acquired through simultaneous imaging, thus eliminating the requirement for additional imaging. We subsequently verified the effectiveness of this subtraction method for improving SLN visibility of breast cancer by evaluating two phantoms constructed based on clinical data.

MATERIALS AND METHODS

Original phantoms

We constructed two original phantoms to evaluate the subtraction method.

The first was a combination (CB) phantom (CB phantom) that imitated the injection site and SLNs. The sources in the CB phantom that imitated the injection site and SLNs are hereafter referred to as CBIS and CBLN, respectively. CBIS measured 20 mm in diameter and contained 15 MBq of ^{99m}Tc -pertechnetate. The CBLNs each measured 10 mm in diameter and contained either 29 kBq (low count) or 58 kBq (high count) of ^{99m}Tc -pertechnetate.

The second was a multi-lymph node phantom (MT phantom) intended to imitate SLNs with various levels of radioactivity. The source in the MT phantom that imitated SLNs is hereafter referred to as MTLN. The 10 MTLNs each measured 10 mm in diameter. The ^{99m}Tc -pertechnetate radioactivity levels ranged from 1/10 (approximately 1.5 MBq) to 1/5120 (approximately 3 kBq) of the CBIS radioactivity through a 10-step 1:1 serial dilution.

In the phantoms, small containers with plastic caps were used to imitate the injection site and SLNs and were fixed on an acrylic board. Figure 1a and 1b show the source layout and radioactivities of the CB and MT phantoms. These phantoms were placed between models intended to imitate the human body, as shown in Figure 1c. The thicknesses of these models were categorized as obesity, normal, and leptosome to

elucidate the effects of attenuation in the posterior view on various body types. The thicknesses were determined based on a random sampling of chest computed tomography (CT) images of 50 patients. Since chest CT images are routine image, it was conducted in accordance with the comprehensive prior consent and it was approved by the institutional ethics committee of our institution. Table 1 shows the thickness and material of each model.

Figure 1: Source layout of the two phantoms and the phantom disposition diagram during imaging. (a) For the combination (CB) phantom, the CB phantom injection site (CBIS; center) is 20 mm in diameter and contains 15 MBq of ^{99m}Tc -pertechnetate. CB phantom lymph nodes (CBLNs; both sides) are 10 mm in diameter and comprise 4 pieces each in horizontal direction at intervals of 10 mm from the periphery of CBIS. The sources contain 29 kBq (right side) and 58 kBq (left side) of ^{99m}Tc -pertechnetate. (b) For the multi-lymph node (MT) phantom, the MT phantom lymph nodes (MTLNs) are 10 mm in diameter. The ^{99m}Tc -pertechnetate radioactivities in the MTLNs ranged from 1/10 (approximately 1.5 MBq) to 1/5120 (approximately 3 kBq) based on the radioactivity of CBIS through a 10-step 1:1 serial dilution. These MTLNs were ordered from top left to top right and bottom left to bottom right. (c) Regarding the disposition of each phantom model, each part is composed of a breast surface (gray), either of the CB phantom or of the MT phantom (black), breast (gray), lung field (light gray), and soft dorsal tissue (gray), as shown from above. The thickness of each model was changed to represent different body types for studying the effect of attenuation in the posterior view.

Table 1: Thicknesses of phantom components for each body type.

Phantom parts	Materials	Thickness of phantom parts (mm)		
		Leptosome	Normal	Obesity
Surface of breast	Water equivalent phantom	10	10	10
Breast (soft tissue)	Water equivalent phantom	10	25	50
Lung field	Sponge	90	110	130
Soft tissue of back	Water equivalent phantom	10	25	40

Imaging

Phantoms were imaged with a dual-head γ -camera (GCA7200A/UI; Toshiba Medical Systems Corp., Otawara, Japan). The collimators were equipped with a low-energy high-resolution (LEHR) on the lower detector (posterior view) and low-energy general-purpose (LEGP) on the upper detector (anterior view). Although it is irregular to acquire scintigrams by using a dual-head gamma camera equipped with different kinds of collimators, we have obtained lymphoscintigraphy by using this unique method in the daily clinical practice for more than 10 years and we have interpreted these lymphoscintigrams based on our own responsibility. Despite the 10 kg difference in weight between the two collimators, the manufacturers confirmed that imaging with different collimators would not present a safety issue.

Static images with a matrix of 512×512 (1.08 mm/pixel) were simultaneously acquired for 5 minutes. The original image of anterior view alone was considered the conventional method image in this study.

Procedure for creating the subtraction method image

The posterior view was subjected to horizontal inversion processing. Afterwards, we corrected a gap caused by a geometrical γ -camera error present between the upper and lower detectors. This gap measured 2 pixels in the horizontal axis direction with this camera. Lastly, the processed posterior view was simply subtracted from the anterior view without requiring the incorporation of a coefficient. As shown in Figure 2, (a, d, and g) left column is anterior (original) images, (b, e, and h) central column is the processed posterior view for subtraction method, and (c, f, and i) right column is images of the subtraction method. A series of this operation was performed using an image processing system attached to the γ -camera (GMS5500A/UI; Toshiba Medical Systems Corp.).

Figure 2: Images and profile curves obtained with the combination (CB) phantom. The upper row shows (a) the conventional method, (b) posterior image of the low-energy high-resolution (LEHR) collimator after horizontal inversion for subtraction, and (c) subtraction method on a leptosome body type model. The middle row shows (d) the conventional method, (e) posterior image of the LEHR after horizontal inversion for subtraction, and (f) the subtraction method on a normal body type model. The lower row shows (g) the conventional method, (h) posterior image of the LEHR after horizontal inversion for subtraction, and (i) the subtraction method for an obesity body type model.

Data analysis

We evaluated the following 4 items to verify the usefulness of the subtraction method: Effect of scattering emitted from CBIS, deterioration of visibility due to subtraction processing, image contrast, and visual evaluation.

Regarding the effect of scattering emitted from CBIS, CBLN visibility was evaluated from the CB phantom image and profile curve. The profile curve was drawn as a continuous plot of counts of regions of interests (ROIs) in the CB phantom. The ROIs measured 10 pixels in width and were measured in the horizontal axis direction, thus incorporating both CBIS and CBLNs.

With respect to the deterioration of visibility caused by subtraction processing, we evaluated whether the subtraction method would deteriorate MTLN visibility relative to the conventional method with regard to the count ratio. The count was obtained from the value of each 5×5 -pixel ROI placed on the centers of the MTLNs.

In regard to image contrast, we compared this parameter in MTLNs using values calculated from the scattering count emitted from CBIS and MTLNs counts because the

phantom image could not discriminate the true SLN count and the background count. Contrast was calculated using the following equation:

$$C = (SLN - BG) / (SLN + BG): \text{(Eq. 1)},$$

where C represents contrast, SLN represents the mean count in MTLN ROIs, and BG represents the mean count in scattering ROIs from CBIS. We determined the BG by placing 5×5 -pixel ROIs from 10 pixels in the periphery of CBIS to 100 pixels at 10-pixel intervals in the vertical axis direction. For SLN , we placed 5×5 -pixel ROIs at the centers of the MTLNs.

In terms of visual evaluation, we evaluated the detectable MTLNs using MT phantom images created by adding the counts and noise from BG ROIs at a distance of 20 pixels from CBIS using ImageJ software (US National Institutes of Health, Bethesda, MD, USA) [19]. In this evaluation discrete, randomly displayed MTLNs were scored using a 3-grade scale (“clear” = 2 points, “faint” = 1 point, and “unclear” = 0 point) by 11 radiological technologists with experience in nuclear medicine techniques.

Statistical analysis

Differences in image contrast according to body type and MTLN visibility were analyzed using the Wilcoxon rank-sum test and McNemar’s test, respectively. The McNemar’s test analysis was performed for two detection samples (clear or faint) versus non-detection samples (unclear) from MTLNs visibility. Differences were considered significant at $p < 0.05$.

Imaging of a clinical case

On the morning of SLN biopsy, the operating surgeon injected tracer (0.3 ml, 18.5 MBq, ^{99m}Tc -phytate) into peritumoral sites. After the surgeon massaged the area for approximately 5 minutes post-injection, lymphoscintigrams were acquired subsequently under the same conditions used for phantom imaging.

Although this acquisition condition is unique, we have routinely obtained lymphoscintigrams by using this method at our institution. Our institutional ethics committee approved the investigation of lymphoscintigrams in accordance with the comprehensive prior consent in this study because the committee determined that these unique lymphoscintigrams were previously obtained in the routine clinical practice, not for the research purpose.

RESULTS

Effect of scattering emitted from the CBIS

Figure 2 shows images and profile curves of the CB phantom obtained using the conventional method as well as the posterior view (LEHR) after horizontal inversion for subtraction process and the subtraction method. The CB phantom image acquired using the conventional method enlarged the surrounding background area and counts because of scattering emitted from CBIS, whereas the subtraction method reduced the

background area and counts. Therefore, with the conventional method, CBLN nearest to CBIS was covered by the scattering, whereas the subtraction method detected this CBLN. The “hot spot peak” of CBLN nearest to CBIS could even be identified from profile curves when the subtraction method was used.

Deterioration of visibility caused by subtraction processing

The MTLN count ratios for the subtraction method relative to the conventional method were 63.0%, 81.6%, and 88.5% with the leptosome, normal, and obesity models, respectively. Figure 3 shows images of the MT phantom obtained with the conventional and subtraction methods. The MTLNs did not disappear from the subtraction method images.

Figure 3: Images acquired with the multi-lymph node (MT) phantom. The upper row shows (a) the conventional method and (b) subtraction method on a leptosome body type model. The middle row shows (c) the conventional method and (d) subtraction method on a normal body type model. The lower row shows (e) the conventional method and (f) subtraction method on an obesity body type model.

Image contrast

Figure 4 shows the MTLNs image contrast to radioactivity ratios based on the distance from CBIS and radioactivity, as determined using the conventional and subtraction methods. Both methods yielded negative contrast at a distance of 10 pixels nearest to CBIS (i.e., the scattering count from CBIS was higher than the MTLN counts). At 20 pixels from CBIS, the conventional method yielded negative values for faint MTLNs ($<1/1280$, approximately 12 kBq), whereas the subtraction method yielded positive values for all MTLNs. Overall, the contrast obtained with the subtraction

method improved as MTLN radioactivity and distance to CBIS decreased. The contrast values obtained with the subtraction method did not differ significantly between the body types ($p > 0.05$).

Figure 4: Images acquired with the multi-lymph node (MT) phantom. The upper row shows (a) the conventional method and (b) subtraction method on a leptosome body type model. The middle row shows (c) the conventional method and (d) subtraction method on a normal body type model. The lower row shows (e) the conventional method and (f) subtraction method on an obesity body type model.

Visual evaluation

Figures 5, 6a, and 6b present images of the visual evaluation, scoring results, and contrast values at a distance of 20 pixels from CBIS. The faintest MTLN, with a radioactivity ratio of 1/5120 (approximately 3 kBq), was difficult to detect using both methods and visibility was not improved with the subtraction method ($p = 0.16$). However, the visibilities from 1/2560 (approximately 6 kBq) to 1/640 (approximately 23 kBq) were significantly improved with the subtraction method ($p < 0.001$). At high levels of radioactivity (not less than 1/320), both methods could detect the MTLNs, and no significant differences were observed between the methods ($p > 0.32$).

Figure 5: Visual evaluation images created using ImageJ software. We added counts and noise corresponding to a distance of 20 pixels from the combination phantom injection site (CBIS) to the multi-lymph node (MT) phantom images. The upper row shows (a) the conventional method and (b) subtraction method on a leptosome body type model. The middle row shows (c) the conventional method and (d) subtraction method on a normal body type model. The lower row shows (e) the conventional method and (f) subtraction method on an obesity body type model.

Figure 6: (a) Results of a visual evaluation obtained from the image shown in Figure 5.

The horizontal axis represents the radioactivity ratios in the multi-lymph node phantom lymph nodes (MTLNs) relative to combination phantom injection site (CBIS) radioactivity (15 MBq). The vertical axis represents the mean visual evaluation values (“clear” = 2 points, “faint” = 1 point, and “unclear” = 0 point) scored by 11 radiological technologists. The statistical analysis was performed using McNemar’s test. (b) Contrast values at a distance of 20 pixels, corresponding to the results of the visual evaluation.

Presentation of two clinical cases

Figure 7 shows the lymphoscintigram findings of two patients with breast cancer, obtained using the conventional and subtraction methods. Only the subtraction method could detect SLNs near the tumor (Figure 7a).

Figure 7: Lymphoscintigraphy data from patients with breast cancer. The upper row shows lymphoscintigram finding via (a) the conventional method and (b) subtraction method in a case where SLN was located near the tumor. The lower row shows lymphoscintigram finding via (c) the conventional method and (d) subtraction method in a case where SLN was located away from the tumor.

DISCUSSION

The aim of lymphoscintigraphy is to present a clear image of SLN locations to surgeons. Mariani *et al.* [4] reported that scattering increases the difficulty of SLN detection near a tumor. De Cicco *et al.* [2] reported that approximately 0.1% of the injected radioactivity is retained per lymph node when a tracer is injected into the peritumoral parenchyma. Therefore, a prime disadvantage of lymphoscintigraphy is that

scattering emitted from the injection site could complicate visibility and possibly cover SLNs. This phenomenon is especially problematic for faint and small-sized SLNs near injection sites. To address this problem, we devised our subtraction method.

On CB phantom images, when we measured scattering counts from the same area as the CBLN nearest to CBIS in a vertical axis direction that did not contain CBLN counts, the conventional and the subtraction method yielded counts of 99 and 14, respectively. This result was obtained by reducing the area rich in scattering emitted from CBIS through subtraction of the posterior view from the anterior view with the subtraction method. On the other hand, the CBLN image counts were approximately 210 (58 kBq) and approximately 60 (29 kBq). Therefore, for a hot spot of 29 kBq, the subtraction method could detect the CBLN nearest CBIS because the CBLN counts were higher than the BG counts. In contrast, the conventional method could not detect the CBLN because the BG counts were higher. For a hot spot of 58 kBq, the CBLN counts were higher than the BG counts with both methods. However, visibility of the conventional method was reduced by low contrast because the CBLN counts are only about double the background counts.

Generally, dual-head γ -camera imaging is performed using identical collimators for both the anterior and posterior views. In breast cancer cases evaluated using the same collimator, the foot of the posterior-view CBIS peak is extended by the effect of a body thickness span and scatter because the target (injection site) is located on the front of the body. When the CB phantom profile curve obtained with an identical collimator pair is superimposed, as shown in Figure 8d and 8g, the posterior view curve is higher than the anterior view at an area corresponding to scattering at the foot of the CBIS peak. If image was subtracted by identical collimator, subtraction at the foot of the CBIS peak becomes excessive. An excess following subtraction causes the periphery of CBIS to lack a ring shape, as shown in Figure 8f and 8i. Although the image count of the area becomes zero, the calculation value from actual counts becomes negative, as shown in Figure 8e and 8h. In the results obtained with a normal body type, the area counts had a maximum value of -843 when both collimators were LEGP, with CBLN counts of approximately 210 (58 kBq) and approximately 60 (29 kBq). Accordingly, even if the CBLN contains some radioactivity, all or part of the hot spot disappears on the image when identical collimators are used because the hot spot is offset by negative counts. These findings confirm that for the subtraction method, the lower collimator requires a higher resolution than the upper collimator in order to suppress this extension of the CBIS peaks.

Figure 8: Images and profile curves generated using differences in the combinations of collimators obtained on a normal body type with a combination (CB) phantom. The upper row shows (a) the fusion profile curves of the anterior view (solid line) and posterior view (dashed line), (b) the profile curve subtracted from the actual count values, and (c) the image generated with the subtraction method. Similarly, the middle row shows (d) the fusion profile curve, (e) the profile curve after subtraction from actual count values, and (f) the image when both collimators were low-energy general-purpose (LEGP). The lower row shows (g) the fusion profile curve, (h) profile curve after subtraction from actual count values, and (i) the image when both collimators were low-energy high-resolution (LEHR).

Tsushima *et al.* [16] reported the appearance of star-shaped artifacts caused by septal γ -ray penetration, which could impair the visualization of SLNs located near the tumor. Based on this report, the routine imaging in authorial institution is using a LEGP with a thick septal to suppress the appearance of artifacts. Accordingly, to acquire images with the subtraction method, the LEHR, which has a higher resolution than the LEGP, was selected as the lower collimator. When the profile curves of the CB phantom obtained with this combination were superimposed, the curves coincided at an area corresponding to scattering at the foot of the CBIS peak, as shown in Figure 8a. When the full width at tenth maximum (FWTM) of CBIS was measured, subtraction of the posterior view with LEHR from the anterior view with LEGP yielded the value closest to zero because the respective values of the anterior and posterior view were 22.2 and 32.0 mm on LEHR images and 24.4 and 39.0 mm on the LEGP images. These results indicated that subtracting the posterior view from the anterior view eliminated only an

area rich in scattering, and thus the subtraction method could detect SLNs near injection site and covered by scattering.

Furthermore, the subtraction method demonstrated that SLNs do not disappear during subtraction because the MTLNs counts were retained to a level of at least 63.0 %, compared with the conventional method. Two factors might explain this result. The first factor was caused by a difference in sensitivity between the LEGP and LEHR collimators. When the MTLN counts for the anterior views were compared between collimators, the LEGP had an approximately 1.6-fold higher sensitivity than the LEHR. A second factor was caused on the basis of a distance-related attenuation difference between the detectors and a photon absorption difference related to passage through the human body in the anterior and posterior views. As the lymph nodes near the injection site affecting visibility are located at the side of the upper detector (anterior view), the MTLN count of posterior view will be lower than the anterior view because of attenuation and absorption. Even in subtracted images, the MTLN will retain detectable radioactivity because of the difference in counts caused by these factors.

Image contrast was improved with the subtraction method, except for MTLNs located at a distance of 10 pixels, as the radioactivity and distance to CBIS decreased. Detection of MTLNs at a distance of 10 pixels was not improved by the subtraction method because the system resolution of the γ -camera could not distinguish the effect of direct radiation at the injection site itself from scattering. In addition, MTLNs located far from the injection site or those with counts considerably higher than the background were not affected by scattering and thus did not benefit from the subtraction method.

In a visual evaluation of MTLNs at a distance of 20 pixels, a significant difference in detection was observed from 1/2560 to 1/640. There was no significant difference in the visual evaluation of MTLNs with ratios of 1/320 or higher because the conventional method could detect these counts that were considerably higher than the scattering counts. In contrast, neither method could detect the faintest MTLNs (1/5120), which had very low counts.

Contrast values of no less than 0.44 in the conventional method and no less than 0.75 in the subtraction method were capable of detecting MTLNs, according to the visual evaluation results. The detectable contrast value increased with the subtraction method because the visual stimulation yielded by the subtraction method became weak at overall counts lower than those required for the conventional method at equal levels of image contrast.

In the phantom study, the subtraction method was shown to be useful for the detection of faint SLNs near the injection site, regardless of body type.

In breast cancer, axillary lymph nodes are considered the most important area for lymphoscintigraphy. However, injection into the C region nearest axillary lymph nodes is most affected by scattering. As breast cancers arise most frequently in the C region, it is very important to improve SLN visibility in that region by reducing the effect of scattering.

Previous studies reported similar results. For example, several papers [8-12] reported that modifying the imaging position improved the accuracy of SLN detection. As these methods increased the distance between the C region and axilla by modifying the imaging position, scattering from the injection site could be avoided. In addition, other methods, including incorporation of a lead shield [7], changes in the acquisition energy window [18], and collimators [14-16], were reported in several papers. These methods were performed with the intent to directly reduce scattering at the injection site. Although any of these methods could enhance SLN visibility by reducing the effect of scattering, these methods required additional imaging to achieve this aim. Additional imaging has the disadvantage of placing burdens on routine workers and patients. In contrast to these previously reported methods, the subtraction method requires no additional imaging and is thus advantageous. Furthermore, the subtraction method can be easily used in the absence of special devices, as only the posterior view is subtracted. Generally, lymphoscintigraphy imaging does not require the posterior view; acquisition of only the anterior view is considered sufficient because the target in breast cancer cases is located on the front of the body. Even if the posterior view is acquired via simultaneous imaging with a lower detector, this is simply done according to imaging protocol habits. Our facility has acquired simultaneously lymphoscintigrams as routine imaging using a dual-head camera since before this study. A new idea came to us that it utilizes posterior view for elimination of scattering through routine work. We focused on the utilization of this posterior view for the subtraction method.

Another advantage of the subtraction method is its ability to present conventional method images at identical positions, as the imaging protocols are conducted simultaneously. Therefore, if a surgeon requested to see both the subtraction and conventional method images, the subtraction method could satisfy this request because it can advantageously present both images.

Lastly, although the results from the subtraction method yielded improved SLN visibility, as shown in Figure 7a and 7b, this is only true for SLNs near the injection site. One disadvantage of the subtraction method is the weak visual stimulation due to count reduction, which causes a deterioration in the SLN visibility not affected by scattering (i.e., distal from the injection site), as shown in Figure 7d relative to Figure 7c. For this reason, we recommend the presentation of both images, even if surgeons request to view only one type of image. This disadvantage of the subtraction method can be overcome by presenting both images.

CONCLUSIONS

The subtraction method yielded improved SLN visibility near the injection site through a quantitative evaluation of phantom images. Using the subtraction method, both subtraction and conventional images can be acquired simultaneously in a single imaging session, and subtraction image can be easily created.

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