Computer-Aided Detection Scheme for Sentinel Lymph Nodes in Lymphoscintigrams using Symmetrical Property Around Mapped Injection Point

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Abstract It is difficult to detect sentinel lymph nodes (SLNs) around an injection point of radiopharmaceuticals mapped in lymphoscintigrams. The purpose of this study was to develop a computer-aided detection (CAD) scheme for SLNs by a subtraction technique using the symmetrical property in the mapped injection point. Our database consisted of 78 lymphoscintigrams with 86 SLNs. In our CAD scheme, the mapped injection point of radiopharmaceuticals was first segmented from the lymphoscintigram using a gray-level thresholding technique. Lymphoscintigram was then divided into four regions by vertical and horizontal straight lines through the center of the segmented injection point. One of the four divided regions was defined as the target region. The correlation coefficients based on pixel values were calculated between the target region and each of the other three regions. The region with the highest correlation coefficient among three regions was selected as the similar region to the target region. The values of pixels on the target region were subtracted by the values of the corresponding pixels on the similar region. This procedure

was repeated until every divided region had been used as target region. SLNs were segmented by applying a gray-level thresholding technique to the subtracted image. With our CAD scheme, sensitivity and the number of false positives were 95.3% (82/86) and 2.51 per image, respectively. Our CAD scheme achieved a high level of detection accuracy, and would have a great potential in assisting physicians to detect SLNs in lymphoscintigrams.

Keywords Computer-aided detection · Lymphoscintigram · Sentinel lymph node · Image subtraction

Introduction

Sentinel lymph node (SLN) biopsy is an effective diagnostic method for examining whether breast cancer has metastasized to axillary lymph nodes [1–3]. For the SLN biopsy, it is necessary for physicians to identify the locations of SLNs in a patient. The radioisotope (RI) method is known as one of the useful techniques for identifying the locations of SLNs based on the characteristic that injected radiopharmaceuticals accumulate in SLNs [4–6]. In the RI method, physicians usually inject radiopharmaceuticals under the nipple the day before breast cancer surgery, and identify SLNs by use of a gamma probe and a gamma counter before the beginning of the surgery. However, it takes a long time to identify them as physicians have to move the gamma probe bit by bit while checking the gamma counter. To shorten the identification time, a lymphoscintigram is sometimes used to make a crude estimate of the locations and numbers of SLNs before breast cancer surgery [7, 8].

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Although physicians try to detect SLNs in lymphoscintigrams, it is not so easy, since the mapped injection point appears as area with very strong activity (high pixel values) due to the remaining radiopharmaceuticals around the injection point. Therefore, detecting the SLNs in lymphoscintigrams is very difficult especially near the injection point. To reduce the influence of these remaining radiopharmaceuticals and to improve the contrasts of SLNs, the radioactivity at the injection point is sometimes shielded by putting a lead plate at the injection point of the patient when taking a lymphoscintigram [9, 10]. However, there is a possibility that the lead plate also shields radioactivity from SLNs near the injection point. As one of the solutions, therefore, a novel image-processing technique for improving the contrasts of SLNs has been desired to detect the SLNs efficiently near the mapped injection point in lymphoscintigrams.

Around the mapped injection point, the gray levels are expected to become almost symmetrical because the radiopharmaceuticals remaining at the injection point radiate gamma rays radially. If there are SLNs near the injection point, they will show as asymmetrical spots near the mapped injection point. Ogawa et al. modeled the mapped injection point by the mean pixel values in each annular area with the width of one pixel centered on the injection point [11]. They then attempted to enhance the SLNs by subtracting the modeled injection point from the mapped injection point in the lymphoscintigram. Although this method could improve the contrasts of the SLNs, there could be many false positives as the differences between the mapped injection point and the modeled injection point could be large since lymphoscintigrams are usually very noisy.

In previous study, many researchers have also developed computerized methods for detection of lesions based on the laterally symmetrical property of normal tissues [12–19]. In those methods, normal tissues were removed while improving the contrasts of the lesions by the subtraction between right and left normal tissues. We considered that SLNs would be enhanced by a subtraction technique using the symmetrical property at the mapped injection point. In order to enhance the SLNs more effectively while maintaining a low number of false positives, we divided the lymphoscintigram into four regions, and obtained a subtracted image between similar regions. We then evaluated the detection performance by applying our CAD scheme to 78 lymphoscintigrams. We finally investigated the usefulness of our CAD scheme by comparing it with three different computerized detection methods.

Materials and Methods

The use of the following database was approved by the Institutional Review Board at our institution. Informed

consent was obtained for the research use of each patient's lymphoscintigrams. The database had been stripped of all patient identifiers.

Materials

Our database consisted of 78 lymphoscintigrams which were obtained by a single injection with technetium colloid [20] (37 MBq). The planar imaging for lymphoscintigram was performed with a gamma camera (E.CAM, LEHR Collimator, Toshiba Medical Systems Co., Odawara, Japan). Acquisition time and energy window were 150 s and 140+60 KeV, respectively. The size of the lymphoscintigram images was 256 pixels by 256 pixels. In the pathology reports for the SLNs using tissues removed in breast cancer surgery, the locations of SLNs were provided using the face of a clock. Their depths were also provided using the breast divided by depth into anterior, middle, and posterior tissues. Two experienced radiologists who referred to the pathology reports determined the locations and the boundaries of the SLNs in lymphoscintigrams by manually adjusting the contrast and density level on a computer monitor. The locations and the boundaries of 86 SLNs in lymphoscintigrams were finally determined as “Gold standard” by the consensus of the two radiologists.

Methods

Figure 1 shows the schematic diagram of our CAD scheme using a subtraction technique based on the symmetrical property in the mapped injection point.

Segmentation of Mapped Injection Point

As one of the characteristics of nuclear medicine, images include many fluctuations which cause much noise. Therefore, lymphoscintigram was first smoothed by using a Gaussian filter [21] in order to reduce the effect of

Fig. 1 Schematic diagram of our CAD scheme using a subtraction technique based on the symmetrical property in the mapped injection point

fluctuations. The filter size and the standard deviation for the Gaussian filter were empirically given as 11×11 pixels and 1.2 by taking into account the sizes of SLNs contained in our database.

The pixel values on the mapped injection point were very high in lymphoscintigrams. We employed a gray-level thresholding technique [22] to segment the mapped injection point. There was a pixel with the highest pixel value in the neighborhood of the center of the mapped injection point. Farther from the center of the mapped injection point, pixel values become much lower, as shown in Fig. 2a and b. To segment the mapped injection point, we varied the threshold value from the highest pixel value to lower pixel values in the gray-level thresholding technique. Figure 2c shows the relationship between the area of the segmented region and the threshold value. The area of the segmented region would increase little by little when the segmented region was within the mapped injection point in original lymphoscintigram. However, the area of the segmented region would increase rapidly if the segmented region protruded from the boundary of the mapped injection point. Therefore, we decreased the threshold value from the highest pixel value to lower pixel values by units of five, and defined the threshold value for the segmentation when the change of the areas of the segmented regions became larger than 100 pixels. Figure 3 shows an example of the segmented image for the mapped injection point by the gray-level thresholding technique.

Subtraction Between Similar Regions

To obtain a subtracted image based on the symmetrical property in the mapped injection point, a lymphoscintigram was divided into four regions by vertical and horizontal straight lines through the center of the segmented injection point, as shown in Fig. 4. The size of divided regions was given to be 50 by 50 pixels. Although the mapped injection point in the lymphoscintigram was expected to become

almost symmetrical, it did not become completely symmetrical due to the diffusion mechanism of pharmaceuticals. To reduce the influence of this unsymmetric nature, we selected a similar region to each divided region. For this comparison, we first put all the divided regions into the first quadrant position, i.e., the divided region in the upper left was reversed right and left, the region in the lower right was moved up and down, and the region in the lower left was displaced right and left and up and down. One of the four divided regions was defined as the target region. The correlation coefficients based on pixel values were calculated between the target region and each of the other three regions. The region with the highest correlation coefficient among three regions was selected as the similar region to the target region, as shown in Fig. 5. Subtracted image was obtained by subtracting the pixel values of the similar region from the target region. In this subtraction, we defined a region of interest (ROI) with the size of 3 by 3 pixels on the similar region at each pixel corresponding to the target region. The pixel value which was closest to that of the corresponding pixel on the target region was selected from the ROI and used in this subtraction [23]. This procedure was repeated until every divided region had been used as target region. Figure 6 shows the subtracted image between each of the four regions and the similar regions. Here, pixel values less than zero in the subtracted image were given as zero.

Enhancement of SLNs

The shape of SLNs tends to be circular in lymphoscintigrams. Therefore, we applied a top-hat transformation [24] to the subtracted images. This procedure can enhance white structures (areas with high pixel values) smaller than the used structure element. In the top-hat transformation, the structure element was given by a circular structure with the diameter of 11 pixels to enhance the SLNs while suppressing fluctuations without circular shape.

Fig. 2 **a** Original lymphoscintigram. **b** Line profile of the pixel values on the vertical straight line through the center of the mapped injection point. **c** Relationship between the area of the segmented region and the threshold value for the gray-level thresholding technique

Fig. 3 Segmented image for the mapped injection point

Detection of SLNs and Evaluation of Detection Performance

The SLNs appeared as regions with high pixel values in the enhanced image. Therefore, SLNs were segmented by applying a gray-level thresholding technique to the enhanced image. We evaluated the detection performance of the proposed method by use of a free-response receiver operating characteristic (FROC) curve [25, 26] which indicates the relationship between true-positive fraction and the number of false positives (FPs) per image when the threshold value is varied in the segmentation of SLNs. When the center of the segmented regions for SLNs was within a true SLN region determined by two experienced physicians, this candidate was considered to have been “truly” detected. When the center of the segmented regions for SLNs was not within a true SLN region, this candidate was considered a false positive. Jackknife FROC analysis method (JAFROC) [27] was also employed to statistically compare the detection performance for our CAD scheme with those for other computerized methods.

Comparison with Other Methods

To evaluate the usefulness of our CAD scheme, we compared our CAD scheme with other three computerized detection methods for SLNs. First, we employed Ogawa's method as a conventional method. In Ogawa's method, the mapped injection point was modeled by the mean pixel

Fig. 4 Lymphoscintigram divided into four regions by vertical and horizontal straight lines through the center of the segmented injection point

values in each annular area with the width of one pixel centered on the injection point. SLNs were enhanced by subtracting the modeled injection point from the mapped injection point in the lymphoscintigram. Second, we employed a computerized detection method based on the subtraction between right and left regions because many researchers have developed computerized detection methods for lesions based on the laterally symmetrical property of normal tissues. In this method, the lymphoscintigram was laterally divided into two regions by a vertical straight line through the center of the segmented injection point. SLNs were enhanced by subtracting pixel values between right and left regions. Finally, we employed a computerized detection method with a top-hat transformation without a subtraction technique because a top-hat transformation is often employed to enhance lesions which have circular shape. Here, the structure element was given by the circular structure with the diameter of 11 pixels, the same as used in our CAD scheme.

Results

Figure 7 shows the FROC curves for our CAD scheme and the three computerized detection methods obtained by varying the threshold value in the segmentation of the SLNs. If the sensitivity of our CAD scheme was 100%, physicians would need only to check the locations of the SLNs detected by our CAD scheme in breast cancer surgery. This would improve not only physicians' identification performance but also would shorten the time for breast cancer surgery. In a CAD scheme for SLNs, therefore, high sensitivity of SLNs is important even if the number of FPs is rather large. Table 1 shows the highest sensitivity and the numbers of FPs per image for each of our CAD scheme and the three computerized detection methods. With our CAD scheme, the highest sensitivity and the number of FPs were 95.3% (82/86) and 2.51 per image, respectively.

Table 2 shows the Figure-of-Merit (FOM) indicated by JAFROC analysis for each detection method. Our CAD scheme had higher FOM than any other detection methods. The difference between our CAD scheme and the computerized method with the modeled inject point ($p < 0.0001$), that between our CAD scheme and the computerized method with the subtraction between right and left regions ($p < 0.0001$), and that between our CAD scheme and the computerized method with a top-hat transformation ($p < 0.0001$) were statistically significant.

Discussion

Some of the SLNs undetected by our CAD scheme existed on the dividing line between regions. Those SLNs were

Fig. 5 Selection of similar region for the target region

divided into two regions by the dividing line, and were suppressed in the subtracted images when the two regions were selected as similar regions with each other. With Ogawa's method based on the subtraction of the modeled injection point, the sensitivity of SLNs was relatively high whereas the number of FPs was large. Because we used the subtraction pixel value within the ROI on a similar region closest to that of the corresponding pixel in the target region, we consider that the effect of large fluctuations in the original image was greatly reduced. As a result, the number of FPs for our CAD scheme was lower than that for Ogawa's method. On the other hand, most of the undetected SLNs existed on the dividing line between regions in our CAD scheme were detected by Ogawa's method. It would

Fig. 6 Subtracted image between each of four regions and the similar regions

be possible to improve the sensitivity by combining our CAD scheme and Ogawa's method in a further study. With the computerized detection method based on the subtraction between right and left regions, the sensitivity of SLNs was relatively low. Although we expected that the sensitivity of SLNs would be improved by varying the threshold value from a high pixel value to a low pixel value in the segmentation of SLNs, the sensitivity was decreased in mid-flow. This reason was that the center of the segmented regions for SLNs had not been within a true SLN region because the segmented regions for SLNs connected to

Fig. 7 Comparison of the FROC curves obtained by our CAD scheme and three computerized detection methods for SLN

Table 1 Highest sensitivity and the number of FPs per image for each of our CAD scheme and the three computerized detection methods

	Highest sensitivity (%)	Number of FPs
Our CAD scheme	95.3	2.51/image
Computerized method with the modeled inject point	94.2	3.32/image
Computerized method with the subtraction between right and left regions	89.5	2.23/image
Computerized method with a top-hat transformation	83.7	2.89/image

nearby FPs. This result would indicate the influence of a not completely symmetric mapped injection point could not be decreased by using the subtraction between right and left regions. In order to investigate the usefulness of subtracting the mapped injection point, we also evaluated the detection performance of the SLNs by a computerized detection method based on a top-hat transformation without the subtraction technique. The detection performance of the computerized method was much lower than that of our CAD scheme. This result implies that it is hard to enhance the SLNs with very low contrast on a sharp gradient in the mapped injection point by a top-hat transformation without the subtraction technique. Therefore, it would be necessary to subtract the mapped injection point in the study for detection of SLNs.

All of undetected SLNs by each of our CAD scheme and three detection methods were SLNs which existed in the area within a radius of 3 cm from the injection points which had been strongly influenced by the remaining radiopharmaceuticals. In a CAD scheme for SLNs, it would be more important to detect SLNs in such area since detecting them is very difficult for physicians. In such area, therefore, we compared the detection performance for our CAD scheme with those for other three detection methods. Table 3 shows the FOMs indicated by JAFROC analysis in the area within a radius of 3 cm from the injection points. Our CAD scheme had higher FOM than any other detection

Table 3 FOMs indicated by JAFROC analysis in the area within radius of 3 mm from the injection points

	FOM
Our CAD scheme	0.656
Computerized method with the modeled inject point	0.478
Computerized method with the subtraction between right and left regions	0.497
Computerized method with a top-hat transformation	0.290

methods. The difference between our CAD scheme and the computerized method with the modeled inject point ($p<0.0001$), that between our CAD scheme and the computerized method with the subtraction between right and left regions ($p<0.0001$), and that between our CAD scheme and the computerized method with a top-hat transformation ($p<0.0001$) were statistically significant.

There are some limitations to this study. First, we used only lymphoscintigrams obtained by a single injection. When the tumor extent is wide, radiopharmaceuticals are injected in a patient at more than one point such that the injection points surround the tumor. If the distances between the injection points are far, it would be possible to detect SLNs by applying the proposed method to each of the mapped injection points. However, if the distances between the injection points are close, the distributions of the activity would not have the symmetrical property at the mapped injection points due to their influence on each other. The computerized detection method for lymphoscintigrams obtained by more than one injection is another research area which would require further investigation. Second, we used lymphoscintigrams which were obtained by dual energy window (140+60KeV) simultaneous collection. In our institution, the energy windows of not only 140 KeV but also 60 KeV was used for mapping a body contour in order to confirm the relationship between the body and the locations of SLNs more correctly. There are also medical institutions in which lymphoscintigrams are obtained by use of only a high energy window to improve the visibility of SLNs. The difference in the image properties between lymphoscintigrams for single energy window and those for dual energy windows would be large. However, we believe that the conclusion of this study would not be changed substantially because the mapped injection point becomes almost symmetrical even if the conditions for taking lymphoscintigrams have been changed. Third, our database used in this study was small. Further studies are required with the use of large data sets to evaluate our CAD scheme for detection of SLNs in lymphoscintigrams. In the further study, we also need to evaluate the usefulness of this CAD scheme in assisting physicians to detect SLNs in lymphoscintigrams.

Table 2 FOM indicated by JAFROC analysis for each detection method.

	FOM
Our CAD scheme	0.801
Computerized method with the modeled inject point	0.731
Computerized method with the subtraction between right and left regions	0.730
Computerized method with a top-hat transformation	0.626

Conclusion

In this study, we developed a CAD scheme for SLNs in lymphoscintigrams by using a subtraction technique based on the symmetrical property in the mapped injection point. The influence of the not completely symmetrical property on the mapped injection point was able to be decreased by using a subtraction method between similar regions. Physicians would be able to identify the SLNs efficiently in lymphoscintigrams by taking into account the detection results of our CAD scheme as a second opinion.

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