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Chapter XV

Breast Cancer Imaging: Image Overlay Navigation Surgery with Fluorescence Imaging in Patients with Breast Cancer

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Abstract

Background: Sentinel lymph node (SLN) identification for early breast cancers became a routine procedure in breast surgery. We introduce the image overlay navigation surgery with fluorescence imaging of indocyanine green (ICG) to obtain safe and accurate identification of SLN and resect the breast cancer with adequate margins.

Materials and Methods: Between October 2008 and December 2009, this study enrolled 50 patients with a breast tumor less than 2 cm in diameter. Initially we obtained three-dimensional (3-D) imaging from multidetector-row computed tomography (MD-CT) by volume rendering. It was projected on the patient's operative field with the clear visualization of lymph node (LN) through projector. And then ICG was injected subdermally in the areola. Subcutaneous lymphatic channels draining from the areola to the axilla were visible by fluorescence imaging produced by Photodynamic eye (PDE) immediately. Lymphatic flow was reached after LN revealed on 3-D imaging. After

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incising the axillary skin on the point of LN mapping, SLN was then dissected under the guidance of fluorescence imaging with adequate adjustment of sensitivity and 3-D imaging.

Results: The location of breast cancer and SLN were revealed on the operative field in all patients. Lymphatic channels and SLN were also successfully identified by PDE. And the sites of skin incision were also identical with the LN being demonstrated by 3-D imaging in all patients. The mean number of SLN was 2.7. The image overlay navigation surgery made visually easy to identify the location of SLN from the axillary skin even in obese patients. There were no intra- or postoperative complications associated with SLN identification.

Conclusions: This combined navigations of fluorescence and 3-D imagings revealed more easy and effective to detect SLN intraoperatively. The image overlay navigation surgery will be applied to the various surgical fields to understand the surgical anatomy and avoid the intraoperative complications.

Keywords: Image overlay surgery, sentinel lymph node biopsy, breast cancer, navigation surgery, fluorescence imaging, indocyanine green

Introduction

Sentinel lymph node biopsy (SLNB) of the patients with breast cancer was introduced by Krag et al. [1] using a radioactive colloid in 1993, consecutively followed by Giuliano et al. [2] using a blue dye in 1994. Recently, many studies have reported the usefulness of SLNB including high detection rate, low false negative rate and the avoidance of axillary lymph node dissection [3-8]. The combination method of radioactive colloid and dye showed high detection and low false negative rates in SLNB [9-11]. However, it needs the learning curve of procedural skill by dye alone and the equipment of nuclear medicine facilities by radioactive colloid. Furthermore, the lymphatic flow to SLN is uncertain during SLNB in the method of dye or radioactive colloid. From those findings, Kitai et al. [12] reported the SLNB of visible lymphatic pathway using an indocyanine green (ICG). We also confirmed that their method was feasible and safe for an intraoperative detection of SLN allowing real-time observation without any need for training, and obtained high detection and low false-negative rates [13, 14]. Therefore, to obtain easy, immediate and accurate identification of SLN and reveal the location of breast cancer during surgery, we introduced a novel approach for SLN identification by fluorescence imaging using ICG and image overlay navigation surgery in patients with breast cancer.

Patients and Methods

All had breast cancer that had been histologically confirmed by aspiration biopsy cytology of lesions smaller than 2 cm without axillary lymph nodes involvement, and were scheduled to receive standard care in accordance with the designated clinical pathway. This study was approved by the Institutional Review Board of Dokkyo Medical University.

Informed consent was obtained from all patients. Patients with a history of allergy to iodine or shellfish were excluded from the study.



Figure 1. Micro projector connecting with a personal computer was setting in the operation room.



Figure 2. The image on the skin surface was adjusted itself to the size of patient according to the site of nipple and the line of lateral edge of major pectoral muscle.



Figure 3. Lymphatic flow was easily recognized on the skin surface of the patient toward LN revealed on 3-D imaging.

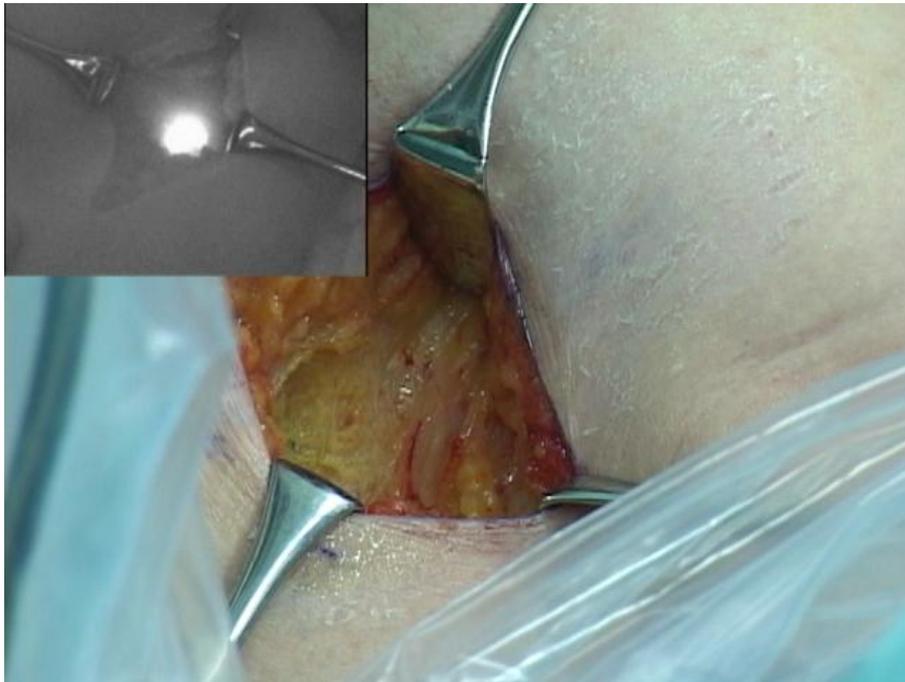


Figure 4. SLN was dissected under the guidance of fluorescence imaging with adequate adjustment of sensitivity.



Figure 5. The PDE was used to confirm whether or not the resected SLNs were fluorescent.

Initially we obtained 3-D imaging from MD-CT by volume rendering of Osirix imaging software (DICOM viewer, Macintosh, Apple Inc., U.S.A.). Its software can be purchased on free by the download from the web site of Apple Macintosh. 3-D image was projected on the operative field of the patient's chest with the clear visualization of LN through the micro projector (M-pro 110; 115x50x22mm, 152g, Sumitomo 3M, Tokyo, Japan) connecting with a personal computer (Figure 1). The image on the skin surface was adjusted itself to the size of patient according to the site of nipple and the line of lateral edge of major pectoral muscle (Figure 2). And then 1ml (5mg) of ICG (Daiichi-Sankyo Pharmaceutical, Tokyo, Japan) was injected subdermally in the areola. Subcutaneous lymphatic channels draining from the areola to the axilla were visible as a fluorescence imaging produced by PDE (Photodynamic eye, Hamamatsu Photonics Co., Hamamatsu, Japan) (Figure 3) [4] immediately. This apparatus is equipped with a light-emitting diode that produces light with a wavelength of 760 nm, and also a charged-coupled device (CCD) camera with a filter. Lymphatic flow was reached after LN revealed on 3-D imaging of the patient and we draw it on the skin to confirm the accurate location of SLN. In a case of invisible lymphatic flow to SLN, the surface of the breast or axillary skin was compressed by a transparent hemisphere device to observe the lymphatic flow. After incising the axillary skin on the point of LN mapping of the patient, SLN was then dissected under the guidance of fluorescence imaging with adequate adjustment of sensitivity and 3-D imaging (Figure 4). The PDE was then used to confirm whether or not the resected SLNs were fluorescent (Figure 5). All LNs showing fluorescence were investigated for the presence of metastasis in the pathology department intraoperatively.

Results

Between October 2008 and December 2009, this study enrolled 50 patients with a tumor less than 2-cm in diameter and no axillary lymph nodes involvement preoperatively. The set-up time consisting of the connection of personal computer, setting of the micro projector and the adjustment of 3D-image on the patient's operation field took 3-8 min (mean: 5.3 min). Lymphatic channels and SLN were successfully identified by PDE in all patients (detection rate: 100%). And the sites of skin incision were also identical with the LN being demonstrated by 3-D imaging in all patients. The mean number of SLN was 2.7 (range: 1-5). Seven patients (14.0%) were found to have lymph node metastases pathologically. The image overlay navigation surgery was visually easy to identify the location of SLN on the axillary skin even in obese patients. The adjustment of sensitivity of PDE and the image overlay navigation provide with the reduction of operation time. The mean procedural time of SLNB was 9.8 min (range: 6-15). The adjustment of sensitivity of PDE was ranged from 20 to 25% to identify the SLN. Furthermore, the compression of the axillary skin by a transparent hemisphere device was effective to identify the location of SLN in non-obese patients. However, 15 patients (30.0%) who had BMI more than 30 kg/m² were still invisible on the axillary skin after the compression by PDE alone. The combination of image overlay navigation using 3D-image was very helpful for those patients to identify the location of SLN. There were no intra- or postoperative complications associated with SLN identification and ICG itself. ICG tattooing around the areola disappeared spontaneously within two weeks.

Discussion

Image overlay means a display technique that superimposes medical images over the direct view of viewer in the real world. The images are transformed in real-time so they appear to the user to be an integral part of the surrounding environment. By using an image overlay with 3-D medical images such as computed tomography (CT) reconstructions, surgeons can visualize the data 'in-vivo', exactly positioned within the patient's anatomy, and potentially enhance the surgeon's ability to perform a complex procedure [15]. Furthermore, by localizing the targeted lesion and the critical lesion that should be avoided, the surgical navigation helps to achieve effective and safe surgery while minimizing the invasiveness of the surgery [16]. Therefore, we applied the image overlay navigation system to obtain safe and early identification of SLN and resect the breast tumor with adequate margins for the patients with breast cancer.

Recently 3D-images have been relatively easy reconstructed from CT, magnetic resonance imaging or ultrasonography. The guidance of 3-D ultrasound image is very helpful for surgeons in determining the resection line of breast conservation surgery according to the superimposed image [17, 18]. However, there are some unresolved problems consisting of the low quality of image due to some particular noise causing by two-dimensional ultrasound image, the requirement of prolonged creation time of 3-D image and the elasticity of the breast. To solve those problems, we reconstructed 3D-CT image by the volume rendering of Osirix. It provides with high quality of image and immediate reconstruction of 3-D imaging and free of charge from web site. Liao et al. [16] reported an autostereoscopic image overlay

technique that is integrated into a surgical navigation system to superimpose a real 3-D image onto the patients via a half-silvered mirror and its use would increase surgical accuracy and reduce invasiveness. And Sugimoto et al. [19] applied image overlay surgery into surgical navigations in gastrointestinal, hepatobiliary and pancreatic surgeries to reduce logistical efforts. Furthermore, we combined the fluorescence imaging of real-time lymphatic flow with the image overlay technique, and could confirm to reach the lymphatic flow to LN superimposed on the patient's axilla. We think that its finding reveals the best navigation system for detecting SLN at this time.

Fluorescence imaging in breast cancer surgery is advantageous in allowing real-time observation of the lymphatic streams on the skin, and superior recognition of lymphatic vessels and LNs in comparison with dye staining alone; furthermore there is no specific need for specialized training for detection of SLNs, and no requirement for a radioisotope facility [12, 13]. However, this method has several problems including the need to turn the shadowless light on and off during the procedure, limitation for detection of SLNs due to easy spreading of ICG through the subcutaneous tissue, its inapplicability to patients with iodine hypersensitivity, and residual dye tattooing that persists for 10 to 14 days [12, 13]. Nevertheless, we think that the advantages of this method outweigh its disadvantages, and that ICG fluorescence imaging provides better outcomes of SLNB.

In SLN identification using ICG, Motomura et al. [20] reported that the SLN detection rate using ICG alone was 73.8%, and that the mean number of SLNs was 1.7. Kitai et al. [12] reported that the SLN detection rate using both ICG and fluorescence imaging was 94% and that the mean number of SLNs was 2.8. The present study showed that the detection rate was 100% and the mean number of SLNs was 2.7. However, with ICG alone, the detection rate was 75.2% and the mean number of SLNs was 2.1. These results were similar to those of Motomura et al. with the use of dye alone without fluorescence imaging. In general, the detection rate using radioactive colloid has ranged from 87% to 98%, with a mean of 92.3 %, and the mean number of SLN ranged from 1.4 to 2.6, with a mean of 1.95 [21-26]. The introduction of fluorescence imaging has yielded a detection rate equal to that of radioactive colloid. Fluorescence imaging using a PDE has high sensitivity for ICG. The combination of fluorescence imaging with a dye is more advantageous for SNNS at institutions that lack suitable facilities for handling radioisotopes. However, the number of SLNs identified using fluorescence imaging in our study was still higher than that achievable using radioactive colloid. We think that unnecessary removal of some LNs is currently a problem with this method. In fact, the number of LNs demonstrated on 3D-imaging ranged from 1 to 3, and these LNs were identical with SLNs visualized by fluorescence. We think that removal of these LNs alone is reasonable in actual clinical practice.

The number of SLNs detected using ICG fluorescence imaging depends on the time taken to identify them. In our series, the number of SLNs in the initial 20 patients was over twice that in the last 20. At the time of introduction of SLNB using ICG fluorescence imaging, identification of SLNs took 20 min or more. However, as the identification time increased, more LNs were found by fluorescence imaging. Because PDE has high sensitivity for ICG, and the injected ICG easily spreads through the subcutaneous tissue including the lymph vessels and LNs during SLNB, even in cases of SLN metastasis. Therefore, we think that the optimum time required for SLN identification is around 10 min, based on the results of recent practice. Furthermore, the outcome also depends on adjustment of the PDE sensitivity. At full power (100%), the PDE showed strong fluorescence from all parts of the surgical field, which

hindered identification of SLNs. Therefore, adjustment of the PDE sensitivity for identifying SLNs ranged from 20% to 25%.

One notable feature was that identification of SLNs in obese patients became relatively easy after the introduction of image overlay navigation. Image overlay surgery with fluorescence imaging is very helpful for residents or medical students to comprehend the lymphatic flow and the correlation between SLNs and axillary vessels. Furthermore, the recognition of the optimal site for a skin incision is identical with that using radioactive colloid and methods such as pinpoint marking. These results represent a considerable advantage of image overlay navigation surgery during SLNB. Recently we have come to consider that image overlay navigation surgery can eliminate the use of indigo carmine with this procedure, as all patients with pathologically positive lymph nodes were recognized by fluorescence imaging, but some were not identified using a vital dye. Although compression of the axillary skin by a transparent hemispheric device was effective for identifying the location of SLNs in non-obese patients, there was an absolute need for the image overlay navigation system in obese patients due to the high rate of invisible nodes (36.0%) in our present series. Because fluorescence can be observed from ICG solution located at a depth of 1 cm in material with optical properties compatible with those human tissue [12], fluorescence through bulky connective tissue in the axilla is invisible at the axillary skin. A further disadvantage of this system is the time required to set-up the projector and personal computer preoperatively. To solve this problem, a dedicated operating room equipped with a we will need an exclusive operating room with a remote-controlled bar and projector will be required.

In conclusion, this combined navigations of fluorescence and 3-D imagings revealed more easy and effective to detect SLN intraoperatively than fluorescence imaging alone. The operator's demand was satisfied with the introduction of image overlay navigation surgery, and it may be practical in the various surgical fields.

Acknowledgment

This study is no significant financial interest or other relationship with the manufactures of any commercial products.

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