Surgery

Evaluation of LIGHTVISION Near-Infrared Fluorescence Imaging System for Surgery

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1. Introduction

Kochi Medical School Hospital is located in the political and cultural center of Tosa Province, an ancient province of Japan. Our hospital lies at the base of Mount Okoh, where the castle of feudal lord Motochika Chōsokabe once stood, and overlooking the River Kokubu, which was mentioned in "Tosa Diary (*Tosa Nikki*)," a famous work of the Japanese author and poet Ki no Tsurayaki. The hospital has 613 beds, 21 medical departments, and 24 medical sections and centers. The hospital is also responsible for leading the prefecture in cancer treatment as a designated prefectural cancer hospital. The Breast Center was established in October 2015 to provide intensive medical care through the collaboration of multiple disciplines, and to support a diverse range of breast cancer care. Of this medical care, breast cancer surgery is becoming increasingly less invasive, and use of sentinel lymph node biopsy has spread rapidly in the pursuit of breast conservation. Common methods of identifying sentinel lymph nodes, which are indicators of breast cancer metastasis, use dyes or radioactive isotopes. However, radioactive isotopes require a radiation controlled area, and using dyes alone requires substantial experience. To counter these issues, the fluorescence method that uses near-infrared fluorescence with indocyanine green (ICG) are spreading in Japan. Our university has developed a system able to visualize fluorescence on a color screen, which has been used in over 600 breast cancer surgeries to date. Given the opportunity to evaluate Shimadzu's LIGHTVISION system **(Fig. 1)** that has been developed to give high definition images (1920 × 1080 pixels), I will describe our experience in using this system.

2. Sentinel Lymph Node Biopsy in Breast Cancer Surgery

Sentinel lymph nodes are the first lymph nodes to receive lymph flow from mammary glands and breast tumors, and are called "sentinel (guard)" lymph nodes due to their role in acting as a lookout for cancer metastasis. When axillary lymph nodes are clinically negative for metastasis in breast cancer cases, surgical dissection of axillary lymph nodes has no positive effect on long-term prognosis. Extended dissection in cases of lymph node metastasis also provides no prognostic improvement. For breast cancer, axillary surgery is performed to check for the presence and number of metastatic lymph nodes and thereby estimate pathologically the tumor burden in the body. In other words, the main aim of axillary surgery is cancer staging. It has been shown prognosis is improved when, regardless of conservation or total removal of the breast, the presence and number of metastatic lymph nodes is used as the basis for determining the need for radiation therapy and area of irradiation, and for strengthening pharmacotherapy by adding drugs to chemotherapy as needed.

Axillary lymph node dissection, which has been

Fig.1 LIGHTVISION

performed for over 100 years, is well known to cause a variety of unpleasant postoperative symptoms with relatively high frequency. These include lymphedema in the upper arm, the need for postoperative rehabilitation to prevent disability related to raising the upper arm, and numbness on the inside of the upper arm. In light of this, the sentinel lymph node biopsy has spread as a means of accurate diagnosis of axillary lymph node metastasis, and of avoiding unnecessary dissection of axillary lymph nodes when no metastasis is present.

3. ICG Fluorescence Method for Sentinel Lymph Node Biopsy in Breast Cancer Surgery

As mentioned earlier, sentinel lymph nodes are normally identified using radioactive isotopes or dyes, where using both methods together results in a higher identification rate. In Japan, many facilities that perform breast cancer surgery have no radiation controlled area and are therefore unable to use radioactive isotopes, which results in many facilities performing dye-guided sentinel lymph node biopsies. Dye-guided identification differs from gamma probe-guided methods that employ radioactive isotopes in that the position of sentinel lymph nodes cannot be estimated from viewing the surface of the body, and therefore a certain degree of experience is needed to maintain a high identification rate. In addition, the dyes commonly used in Japan (indigocarmine and ICG) are low-molecular weight molecules that are not trapped in sentinel lymph nodes but quickly flow into downstream lymph nodes. It is difficult to determine reliably which of multiple lymph nodes that have been dyed blue are sentinel lymph nodes, and often multiple different lymph nodes are removed simultaneously under the impression they are sentinel lymph nodes.

A fluorescence method that applies near-infrared light to ICG and visualizes the fluorescence created by ICG excitation can be used to observe lymph nodes from the body surface, since excited near-infrared light penetrates tissue and allows the user to estimate sentinel lymph node location **(Fig. 2a)**. In people who are thin, this method can even be used to confirm the location of the lymph nodes themselves. Since the fluorescence emitted can also be seen through fascia that covers the lymph node, sentinel lymph nodes can be found quickly by making an incision in the skin and retracting the tissue **(Fig. 3)**. This method can also visualize the network of lymph vessels inside a wound, which allows the user to determine definitively whether the lymph nodes being dissected are sentinel lymph nodes by following lymph vessels that flow into luminous lymph nodes up towards the breast, and confirming no other luminous lymph nodes are present along the lymph vessels. This precludes the need to dissect multiple lymph nodes as performed with the dye-guided method. Also, since lymph nodes with even a very small amount of ICG become visible, metastatic lymph nodes that are

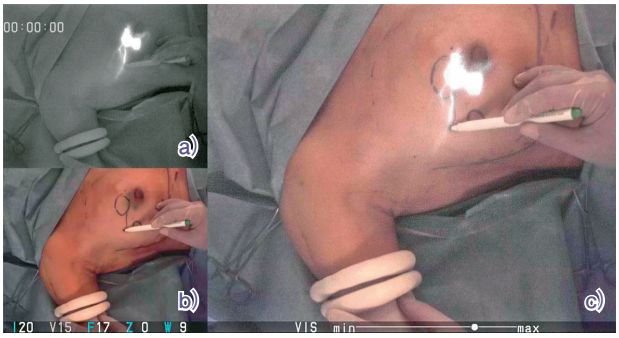
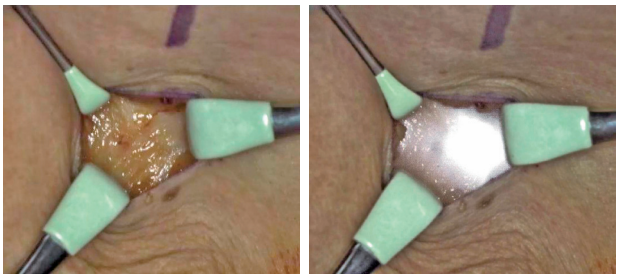


Fig. 2 **a)** Near-infrared fluorescence image. Lymph vessel leading to the armpit is shown on the body surface.
b) Visible image
c) Near-infrared fluorescence image + visible image



a) Visible light screen **b)** Near-infrared fluorescence image + visible image

Fig. 3 Sentinel lymph nodes not visible using dyes (visible light screen) are visible while under the fascia using near-infrared light.

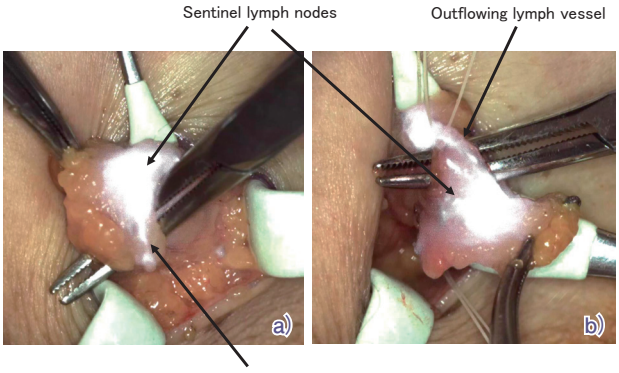


Fig. 4 **a)** Inflowing lymph vessel to be isolated by ligation is lifted with forceps
b) Ligation of outflowing lymph vessel

difficult to identify with either radioactive isotopes or dye can be identified as sentinel lymph nodes with this method.

An issue with this method is that leakage of even a small amount of ICG into the surgical field will cause the entire surgical field to fluoresce, which makes sentinel lymph nodes difficult to recognize with accuracy. To avoid this situation, inflowing lymph vessels must be identified and isolated by ligation before dissection **(Fig. 4a)**. Outflowing lymph vessels must also be isolated by ligation whenever possible to avoid contaminating the wound with ICG after sentinel lymph node dissection, and to observe the wound with the fluorescence imaging after dissection **(Fig. 4b)**.

4. Characteristics and Effectiveness of LIGHTVISION

The near-infrared fluorescence imaging system in current use at our hospital is a non-Shimadzu model that shows weak near-infrared light on a full color background image by combining its ultrahigh-sensitivity CCD camera with a special optical filter that allows near-infrared light to pass but attenuates visible light. As a result, near-infrared light is represented by only one color (white) in images, and this color cannot be changed during use. LIGHTVISION, however, comes with independent high definition image sensors that capture a visible light image and near-infrared image and can perform imaging across a wide range of wavelengths, from visible light to near-infrared light. This allows LIGHTVISION to display both visible and near-infrared light images simultaneously on the same screen in real time **(Fig. 2)** and change the color being used to represent near-infrared light. The color used to represent near-infrared light can be changed in situations such as when light reflecting from fascia causes the background to glow white, making it difficult to distinguish lymph vessels and lymph nodes **(Fig. 5)**. This allows for easy discernment of lymph vessels and lymph nodes.

LIGHTVISION is also able to display so-called high definition (1920 × 1080 pixel) images on a monitor in a landscape orientation. The image acquisition rate of 30 frames/second can also be switched to 60 frames/second as needed, allowing the user to prioritize sensitivity or refresh rate. This permits detailed observation of the network of lymph vessels in a wound and more accurate identification and isolation by ligation of inflowing and outflowing lymph vessels, which is essential for this ICG fluorescence method.

Recently, we have come to understand that when metastasis to sentinel lymph nodes is found but there are 2 or fewer metastatic lymph nodes, there is difference in long-term prognosis or axillary lymph node recurrence between a patient group that undergoes axillary dissection and a patient group in whom axillary dissection is omitted based on breast conservation and postoperative breast irradiation. In Europe and the USA, axillary dissection should not be performed in cases that meet these conditions, and in Japan the number of facilities that omit dissection is also gradually increasing. However, when a patient is found positive for metastasis during surgery and 1/1 or 2/2 sentinel lymph nodes are metastatic on removal of 1 or 2 sentinel lymph nodes, there are worries about whether the case meets those conditions and hesitancy for omitting axillary dissection. At our hospital, sentinel lymph nodes are frozen, a slide is prepared every 2 mm, and if metastasis is found over more than 2 mm during rapid perioperative pathological diagnosis, while viewing the wound with a near-infrared fluorescence imaging, the thread used to ligate the outflowing lymph vessel is pulled, and 2 to 3 additional connecting lymph nodes are removed downstream from the lymph vessel. After this, lymph node metastasis is once again searched for by the same method. When 2 or fewer lymph nodes are diagnosed as metastatic out of examining 3 to 4 lymph nodes, we have improved diagnostic accuracy and based on this decide it is safe to omit axillary lymph node dissection. The ICG fluorescence method requires

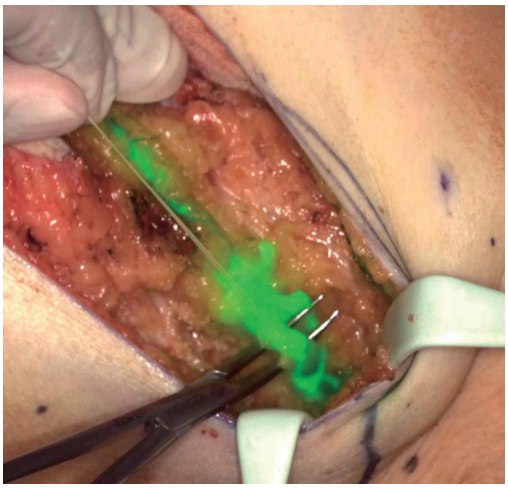


Fig. 5 Sentinel lymph node biopsy with breast removal. Near-infrared light is changed to green for ligation of an inflowing lymph vessel.

advance identification and isolation by ligation of outflowing lymph vessels downstream from sentinel lymph nodes. Since detailed observation of the lymph vessel network is useful for the isolation of nearby lymph nodes, LIGHTVISION, which is capable of capturing fluorescence in high definition, is most suited to playing an effective part in execution of this method.

Conclusion

Sentinel lymph node biopsy is already standard treatment in breast cancer surgery, with Japanese Breast Cancer Society statistics showing approximately half the patients who have surgery undergo a sentinel lymph node biopsy without dissection. We presume that ICG fluorescence method plays a very important role among these patients at facilities that have no radiation controlled area. Among near-infrared fluorescence imaging systems, LIGHTVISION is the only system capable of depicting areas of interest in color and in high definition. We expect LIGHTVISION will become an indispensable tool in future breast cancer surgeries based on the improved accuracy of sentinel lymph node biopsies and improved safety with which axillary lymph node dissection can be omitted in cases positive for lymph node metastasis.

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