SENTINEL LYMPH NODE BIOPSY USING REAL-TIME FLUORESCENCE NAVIGATION WITH INDOCYANINE GREEN IN CUTANEOUS HEAD AND NECK/LIP MUCOSA MELANOMAS

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Abstract: Background. The triple technique (lymphoscintigraphy, patent-blue staining, and a gamma probe) constitutes a reliable method for the sentinel lymph node (SLN) biopsy. However, in head and neck melanomas, a shine-through phenomenon, which occurs because these SLNs are close to the primary focus, is irreversibly problematic. To get around the shine-through phenomenon, this study uses the fluorescence navigation with indocyanine green (ICG) as well as the triple technique.

Methods. ICG is a green dye and can be used as a marker with infrared fluorescence. ICG solution is intradermally injected around the tumor. By using Photodynamic Eye (PDE) intraoperatively, it is possible to observe the injected ICG as SLNs in the fluorescence images.

Results. By use of the fluorescence imaging with ICG, clear identification of the SLN of the case became possible.

Conclusions. We think the fluorescence navigation with ICG will be a useful option for the SLN biopsy in head and neck melanomas.

Keywords: indocyanine green; sentinel lymph node; melanoma; head and neck; shine through phenomenon

It is necessary to conduct sentinel lymph node (SLN) biopsy for a diagnosis of lymph node metastasis of cutaneous primary melanomas located in the head and neck region. The SLN is the first lymph node in the lymphatic basin to be affected by metastatic tumor cells from a primary lesion, and a biopsy here provides a way to avoid elective neck dissection in cases in which there is no metastasis to the SLN.1 When the primary focus is the cutaneous or lip mucosa melanoma, the lymphatic drainage to lymph node groups in the superficial layer of the subcutaneous tissue, such as facial nodes, parotid nodes, submental nodes, submandibular nodes, and superficial lateral cervical nodes becomes important. The triple technique (lymphoscintigraphy and intraoperative mapping with patent-blue staining and a handheld gamma probe) is a reliable method for detecting SLNs in melanoma patients.2 However, in the case of head and neck melanomas, a shine-through phenomenon, which occurs because these SLNs are close to the primary focus, is irreversibly problematic.3–6 In these cases it becomes difficult to measure the radioactivity accurately with a handheld gamma probe because of the closeness of the primary focus to the lymph nodes. To get around the shine-through phenomenon at the head and neck region, this study uses real-time fluorescence navigation with indocyanine green (ICG) as well as the triple technique. ICG is a green dye and can be used as a marker with infrared fluorescence.7 By using a near-infrared (NIR) camera system intraoperatively, it is possible to observe the ICG injected around a tumor as subcutaneous lymphatic drainage and SLNs in the fluorescence images. This report introduces the actual methods as they are applied and used.

CASE REPORT

Patient. A 47-year-old man presented with a malignant melanoma of the upper lip area (Figure 1). The tumor thickness of the nodular region was 2.0 mm. Other lip mucosa and gingiva had melanoma in situ. The patient underwent preoperative lymphoscintigraphy to determine the number, location, and laterality of the nodal basins at risk for metastatic infiltration. The lymphoscintigraphy was performed 2 hours prior to the surgery using technetium Tc 99m phytic acid.8 Intraoperative lymphatic mapping with patent-blue staining was performed using previously described techniques.1 A handheld gamma probe was used to verify that the skin mark made by the operating surgeon corresponded to the area of greatest radioactivity. Through the preoperative lymphoscintigraphy SLNs were identified in the cheek area, in the submandibular area (Figure 2). The SLN in the submandibular...
node was identified and removed; however, because of the shine-through phenomenon, no SLN in the left buccinator node could be identified by the handheld gamma probe. The ICG is dissolved at a concentration of 5 mg/mL in aqueous solution. Having diluted the ICG to 5 mg/mL, 0.1 mL (ICG 0.5 mg) was injected at each of the 4 sites and the total dosage was 0.4 mL (ICG 2 mg). The ICG was injected evenly around a tumor lesion at a distance of 1 mm from the tumor margin (Figure 3). Following this, the SLN in the buccinator node, which initially could not be identified, was identified and removed, again using real-time fluorescence navigation with ICG in the affected area (Figures 4A and 4B).

**Instruments.** The NIR fluorescence imaging system Photodynamic Eye (PDE, Hamamatsu Photonics, Hamamatsu, Japan) is equipped with a light-emitting diode (LED) that emits at the NIR wavelength of 760 nm as excited light, and a charge-coupled device camera as an image detector with an optical high-pass filter in front of the charge-coupled device so that fluorescence signals can be efficiently detected. The working distance (the distance between the camera and the tissue) is from 15 to 25 cm (User manual in PDF, Hamamatsu Photonics). This system consists of a...
camera unit, a controller that operates the camera unit, and a remote controller that controls the LED intensity, video gain, and offset. The fluorescence image is sent to a digital video processor to be displayed on the monitor of a laptop computer in real time. Fluorescence images are continuously observed on the monitor.

**Procedure.** The ICG (Daiichi Pharmaceutical Co., Tokyo, Japan) is dissolved at a concentration of 5 mg/mL in aqueous solution. The ICG is injected at the rate of 0.1 mL (0.5 mg) at every injection site around the tumor. When the tumor lesion is large, as in this case, injection is performed around the nodular lesion at which position the tumor thickness may be expected to be the largest. A 27-gauge needle is used to inject ICG intradermally. Patent-blue is injected intradermally before the ICG injection. The blue dye does not absorb the fluorescence from ICG. ICG is a green dye and can be used as a marker with infrared fluorescence. When a PDE camera unit is trained on the object to be observed after intraderal injection of ICG, it is possible to observe subcutaneous lymphatic drainage and SLNs as fluorescence images in real time. The charge-coupled device camera was wrapped in a sterilized vinyl cover to intraoperatively conduct fluorescence observation. The observation of lymphatic drainage is conducted by the free hand because of its high degree of freedom. With shadowless operation theater light that emits NIR light, which is stronger than the fluorescence of ICG, it is necessary to switch the lights off. However, since room light emits only very little NIR light, switching these lights off is not necessary. A couple of minutes after the ICG injection, lymph nodes can be detected. The lymph nodes that were identified and removed through real-time fluorescence navigation with ICG were measured extracorporeally by a handheld gamma probe, and this is the basis for the final determination of whether they are SLN.

**DISCUSSION**

ICG is a widely used diagnostic reagent that is clinically approved for use in the examination of the hepatic function and cardiac output. The excitation wavelength of ICG is between 750 and 810 nm and generates a fluorescence peak wavelength at 845 nm when it is combined with plasma protein.

Because of its intraoperative usability, the application for SLN biopsy using ICG fluorescence imaging has been reported in recent years. Not only did Kitai et al. report on the effectiveness of SLNB using ICG fluorescence navigation in breast cancer, but also Sevick-Muraca et al. reported that fluorescence imaging is possible with microdoses of ICG (≥10 μg). Kusano et al. reported a new method for sentinel node navigation surgery using ICG fluorescence imaging in gastrointestinal cancer. Moreover, Fujiwara et al. reported that it was effective for SLN biopsies for patients with melanomas at the lower limb or sacral regions. Hojo et al. reported that using both blue dye and ICG improved the sensitivity of identification in SLN biopsies of breast cancer. With patent blue, visualization of lymphatic vessels with the naked eye becomes possible. Finally, the SLN is identified and removed using fluorescence images of ICG that enable excellent detection sensitivity.

In Figure 3, the ICG injected around the tumor can be seen as a green color, but as Figure 4A shows dyes of neither patent-blue nor green color of ICG at the buccinator node that is SLN could be seen visually with the naked eye. However, as Figure 4B shows, the buccinator node can be clearly seen in the fluorescence image that used the PDE device. Based on these facts, we think that the ICG, slightly retained in the SLN, can be detected if we use the fluorescence imaging. Regarding the SLN biopsy at the head and neck region, there are cases in which the naked eye cannot confirm that SLN is dyed blue even when patent blue is injected. We infer that this is because the staining period for patent blue with SLN is short due to the rapid and complex lymphatic drainage at the head and neck region. Considering these, we think the ICG fluorescence imaging is effective in SLN biopsy at the head and neck region.

Although ICG is a safe reagent that has fewer side effects, it has been reported that 0.17% of the cases in which the ICG was administered had side effects, such as experiencing shock (0.02%), nausea (0.08%), and angialgia (0.04%) (Daiichi Pharmaceutical Co., Tokyo, Japan; Instruction manual for ICG). SLN biopsy is required for a diagnosis of lymph node metastasis of cutaneous primary melanomas. Morton et al. introduced SLN mapping with biopsy for the evaluation of patients with cutaneous melanomas of the trunk and extremities. The triple technique (lymphoscintigraphy and intraoperative mapping with patent-blue staining, and a handheld gamma probe) is a reliable method for detecting the SLN in melanoma patients. However, some of the problems with SLN biopsy of cutaneous head and neck melanoma include the complexity of the lymphatic drainage in the head and neck region and the shine-through phenomenon, since the SLN in the head and neck is located close to the primary lesion.

For melanomas located at lips or in the buccal regions, there are many cases in which facial nodes, parotid nodes, submental nodes, submandibular nodes, and superficial lateral cervical nodes are the first lymph node. When performing the SLN biopsy, the shine-through phenomenon will cause significant problems because these first lymph nodes are close to the primary focus. In other words, because of the closeness of the primary focus to the lymph nodes, it becomes difficult to accurately measure the radioactivity with a handheld gamma probe. To get around the shine-through phenomenon at the head and neck
region, this study uses real-time fluorescence navigation with ICG together with the triple technique (lymphoscintigraphy and intraoperative mapping with patent-blue staining and a handheld gamma probe).

In actual operations, lymph nodes, which are identified by using real-time fluorescence navigation with the ICG, are removed, and their radioactivity is measured extracorporeally by a handheld gamma probe, and this is the basis for the final determination of whether they are SLN. This procedure makes it easier to identify the superficial lymph nodes that have been difficult to identify because of the shine-through phenomenon. Preoperative lymphoscintigraphy is necessary to check the location and the number of the SLN in advance.

In conclusion, the real-time fluorescence navigation with ICG can be a useful option for the SLN biopsy in cutaneous head and neck melanomas. For the future, application of this method is planned for a larger patient population to evaluate the validity of the procedure. We believe that this method will be useful for the detection work of the SLN biopsy in cutaneous head and neck melanomas.

REFERENCES


