Validity of Sentinel Lymph Node Biopsy by ICG Fluorescence for Early Head and Neck Cancer

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Abstract. *Aim: This study was designed to assess the validity of sentinel lymph node (SLN) biopsy using either the combination of indocyanine green (ICG) fluorescence and radioisotope (RI) or ICG-alone in SLN mapping for early head and neck cancer patients. Patients and Methods: Nineteen patients received SLN biopsy with the following method. Thirteen patients received SLN biopsy with only RI, 2 patients with only ICG and 4 patients with the combination of ICG and RI. Detection time for each method of SLN biopsy was measured to evaluate the validity of SLN with the combination of ICG and RI. Results: A total of 41 SLNs were identified by RI or ICG. All SLNs identified by ICG could be localized intraoperatively. The number of SLNs identified by the combination of ICG and RI was greater than that of SLNs identified by RI-alone. One of the patients who underwent SLN biopsy by RI-alone was diagnosed with a metastatic lymph node one year later, then underwent neck dissection. Mean detection time for SLN biopsy with ICG or with the combination of ICG and RI tended to be shorter than that of RI-alone. Conclusion: SLN biopsy with the combination of ICG and RI enabled us to identify SLNs more easily and rapidly than by using RI alone.*

Sentinel lymph node (SLN) biopsy has become the most widely used procedure to determine the regional lymph node status of breast cancer (1). SLN biopsy has also been adopted for various other cancers, such as head and neck cancer, gastric cancer and melanoma. Regional lymph node metastases represent the most important prognostic factor for head and neck cancer (2-4). Many trials of SLN biopsy in head and neck cancer have been reported, particularly in early oral cancer, because the risk of latent lymph node metastases is relatively high. The rate of lymph node metastases is reportedly 30% in T2 tongue cancer (5-7). Lymphatic mapping in this region is more difficult than elsewhere due to the intricate anatomy. The surgeon has to rely mainly on preoperative lymphoscintigraphy and the intraoperative gamma ray detection probe. However, the SLN identification rate remains relatively low and the false-negative rate is high (8). An additional method of intraoperative detection is required to improve the identification rate. The blue dye method can reveal SLNs directly by color but this method has certain drawbacks (9-12). Visibility is easily lost with dense fat, intraoperative bleeding or rapid transition.

Lymphatic mapping using radioisotope (RI) is a conventional technique but SLN biopsy using this method shows drawbacks in the head and neck region. SLNs in this area are often located in close proximity to the injection site and a high background signal can hamper sentinel node detection with the gamma ray probe. Moreover, the surgeon has to rely solely on the sound of the probe to detect SLNs because SLNs cannot be visualized with this method.

To overcome such drawbacks, new methods, such as near-infrared (NIR) fluorescence, have started being used in recent times. The material in NIR fluorescence is indocyanine green (ICG), which penetrates human tissues to a depth of 1-2 cm and allows for transcutaneous visualization of SLNs and lymphatic vessels (1). In particular, it allows for intraoperative identification of SLNs with simultaneous coloration and NIR fluorescence. We have already gained experience, as reported on animal experiments, in which the ICG fluorescence method was successfully adapted to the head and neck region (13).

The present study examined the validity of SLN biopsy in patients with head and neck cancer using the combination of ICG fluorescent and RI methods.

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Key Words: Oral cancer, hypopharyngeal cancer, oropharyngeal cancer, radioisotope, ICG fluorescence.

Materials and Methods

Patients. The patients' characteristics are outlined in Table I. Nineteen patients with T1-T2, N0 squamous cell carcinoma of the head and neck treated from August 2005 to December 2012 in our Hospital were included in this study. The mean age of patients was 63.1 years (range, 44-84 years). The underlying pathology was oral cancer in 15 patients, oropharyngeal cancer in 2 patients and hypopharyngeal cancer in 2 patients. Thirteen patients underwent SLN biopsy using RI, 2 patients using only ICG and 4 patients using the combination of RI and ICG.

Informed consent was obtained from every patient preoperatively and this study was approved by the Human Ethics Review Committee of Kyorin University.

RI method. The day before surgery, 1.0 ml of ^{99m}Tc-tin colloid (Japan Mediphysics Company, Tokyo, Japan) was injected submucosally into patients who underwent SLN biopsy using RI with a 27-gauge needle at four spots around the primary tumor. After injection, mouthwash was immediately employed to prevent pooling or swallowing of residual radioactivity by patients (14). About 2 h later, lympho-scintigraphy was performed. SLNs were then localized using a hand-held gamma probe (Neoprobe; Johnson & Johnson Medical, Hamburg, Germany) and the positions of any SLNs identified were marked on the skin preoperatively. The next day, we used the gamma ray probe to detect SLNs intraoperatively. Hot lymph nodes with high radioactivity were considered to represent SLNs and were excised (15).

ICG method. ICG (Daiichi Sankyo, Tokyo, Japan) was prepared and re-suspended in 10 ml of sterile water for injection to yield a 2.5-mg/ml (3.2 mM) stock solution (16). Next, 0.5 ml of ICG was injected submucosally into four spots around the primary tumor and, after 15 min, fluorescing lymph nodes were localized transcutaneously using a NIR fluorescence imaging system (HyperEye Medical System (HEMS); Mizuho Medical, Tokyo, Japan) (Figure 1). Lymph nodes that showed fluorescence at 15 min after injection of ICG were considered to represent SLNs. HEMS was positioned 50 cm above the area. The detection of SLNs appearing as transcutaneous spots of fluorescence on the TV monitor in a dim room was performed before the surgical procedure. If shining fluorescent spots were observed, SLN biopsy was initiated under shadowless light (13).

Combination method of RI and ICG fluorescence. In the combination method for RI and ICG fluorescence, we resected all SLNs detected by either method. SLN biopsy was performed using the HEMS monitor and hand-held gamma probe. Resected SLNs were also confirmed by both instruments (Figure 2).

Measurement of detection time for SLNs. The detection time for SLN biopsy was measured to clarify how SLN biopsy was improved with the new combination method. Detection time was defined as the time from skin incision to extraction of the first SLN. If SLNs were diagnosed as metastasis, neck dissection was performed.

Results

Table II shows the results of SLN biopsy. Nineteen consecutive patients with head and neck cancer underwent SLN biopsy using RI and/or ICG or ICG alone. The mean duration of follow-up was 38.5 months (range=10.7-69.9 months).

Figure 1. *HyperEye Medical System (HEMS) illuminates the ICG with an array of light-emitting diodes (LEDs) and the CCD camera captures the ICG fluorescence images. Then the fluorescence image is shown on the imaging monitor. ICG, Indocyanine green; LED, light-emitting diodes; CCD, charge-coupled devise.*

Identification of SLNs by the RI method. SLNs were detected in all patients (100%). A total of 41 SLNs were identified in all patients and the mean number of SLNs in each patient was 2.2 (range=1-4). SLN biopsy by RI alone was performed for 13 patients, with a mean of 2 SLNs (range=1-4) identified. The radioactivity of lymph nodes was measured intraoperatively by the gamma ray probe and each identified SLN showed high radioactivity (Figure 2). The SLN in one case (Patient 4) was diagnosed as metastatic, thus neck dissection was performed. Conversely, lymphatic metastasis was detected in Patient 1 after one year, therefore neck dissection was performed. After neck dissection, Patient 1 survived without evidence of recurrence for 69.9 months.

Identification of SLNs with the combination of RI and ICG methods or ICG alone. SLN biopsy with the combination of ICG and RI was performed in 4 patients and the mean number of SLNs identified was 3 (range=2-4). SLNs of all patients could be identified by both ICG and RI, while 5 SLNs showed correspondence of high radioactivity and fluorescence. SLNs

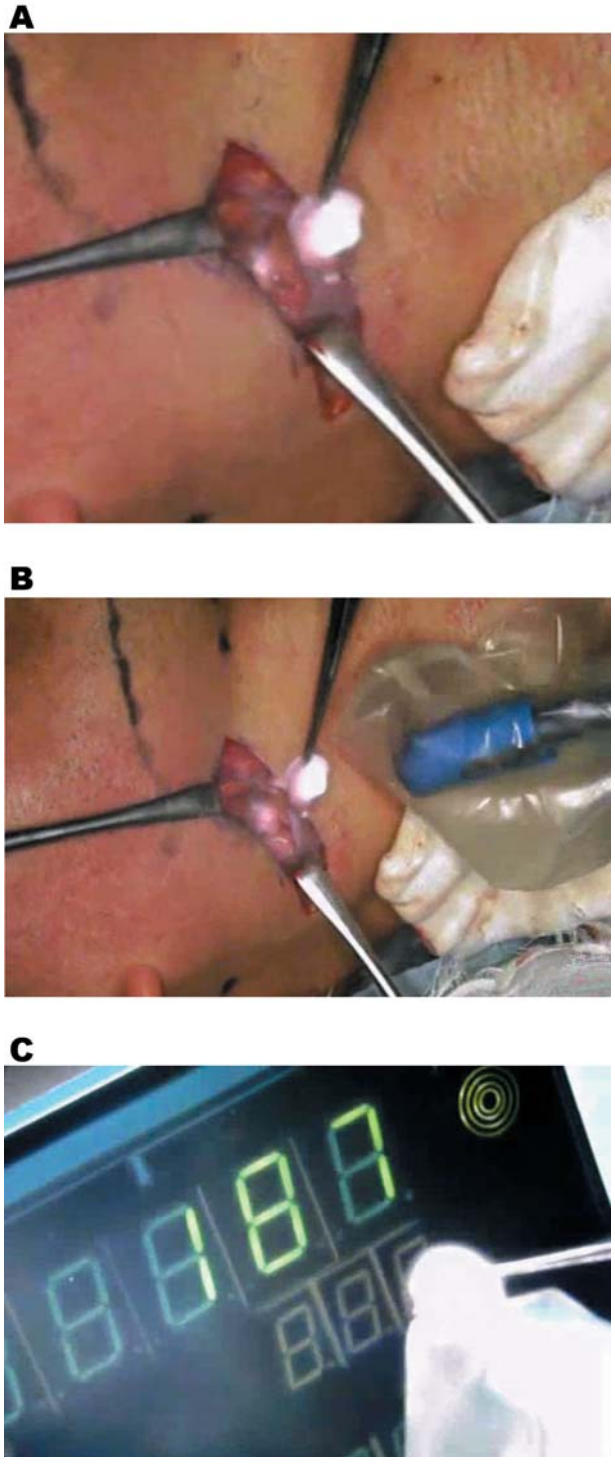

Figure 2. *a) A SLN was visualized on the color image of intraoperative real-time lymphography by HEMS. SLN, Sentinel lymph node; HEMS, HyperEye Medical System. b) Radioactivity of the fluorescent lymph node was measured intraoperatively by the gamma ray probe. Correspondence between high radioactivity and fluorescence was confirmed. c) Radioactivity of the identified SLN was measured by the gamma ray probe intraoperatively. High radioactivity was shown. SLNs were, thus, identified by two methods. SLN, sentinel lymph node.*

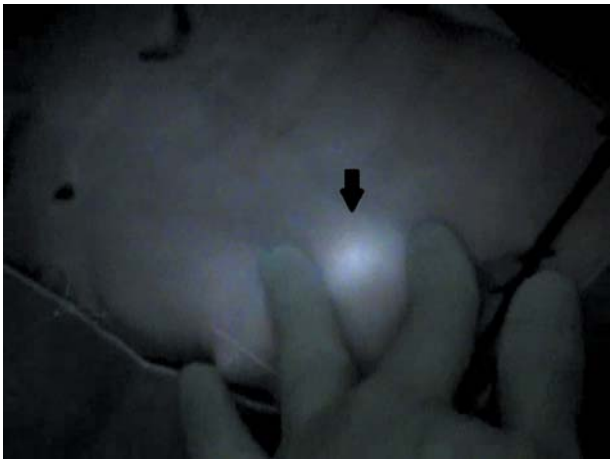

Figure 3.*The fluorescent SLN was visualized transcutaneously by the HEMS camera when the skin over the SLN received pressure. SLN, sentinel lymph node; HEMS, HyperEye Medical System.*

identified by ICG were visualized using the HEMS camera while putting pressure on the skin above the presumptive site of the SLN (Figure 3). Seven additional SLNs were identified by ICG compared to RI. All SLNs identified by RI were also identified by ICG. In Patient 16, four SLNs were detected by ICG but none showed an accumulation of RI. In Patient 14, three additional SLNs were identified and one SLN identified by the combination of ICG and RI was diagnosed as metastasis and neck dissection was, therefore, performed. Patient 14 has since survived with no evidence of recurrence. SLN biopsy using ICG alone was performed in 2 patients, identifying 3 SLNs in total. No metastases were diagnosed.

Accuracy and false-negative rate were 100% (19/19 patients) and 5.3% (1/19 patients), respectively.

Detection time for SLN biopsy. We measured the detection time for SLN biopsy to objectively clarify the improvement of SLN biopsy with the new methods containing ICG. Table III shows the results of detection time for SLN biopsy by all procedures. Mean detection times for SLN biopsy, including the use of ICG and with RI alone, were 19.8±12.6 min and 30.6±11.6 min, respectively (Table III). Detection times with methods containing ICG had a tendency to be shorter than those with RI alone.

No patients showed any adverse reactions or complications caused by the injection of RI or ICG. All patients tolerated the procedure.

Discussion

Morton *et al*. (17) defined the SLN as the first lymph node in a regional lymph node basin that receives lymph flow from a primary tumor. SLN status indicates the lymphatic spread of

the tumor: if the SLN is negative, the other nodes in the same basin are unlikely to contain metastasis, whereas the risk of non-SLN metastasis is significant if the SLN is positive (18). Various methods of SLN biopsy have recently been used, such as blue dye, RI and combination techniques, but various disadvantages remain.

The blue dye method is safe, convenient and cost-effective but shows limitations, such as loss of visibility in dense fat and rapid transit of the dye (19-22). In addition, blue dye cannot provide the location of the SLNs before skin incision because the dye does not penetrate the dermis (23).

RI offers superior tissue penetration but exposes both caregivers and patients to ionizing radiation and can only be detected with a gamma probe, which does not provide the surgeon with visual information. The time window for SLN identification is short because of the short half-life of ^{99m}Tc (6 h) (16). RI is expensive and requires specialist radioactive facilities. Furthermore, RI causes a "shine-through phenomenon" in which radioactivity of the tracer is so strong that radioactivity of the true SLN may be masked when the tracer is injected to the primary lesion (13). As mentioned above, the intricate anatomy of the head and neck region makes SLNs difficult to identify, thus the identification rate of SLNs is not particularly high in this method.

To overcome these disadvantages, ICG has been used to improve the accuracy of SLN detection. ICG is a popular diagnostic reagent that has been clinically approved for use during examination of hepatic function, cardiac output and retinal angiography (20). ICG has a peak absorption wavelength of 760-800 nm when dissolved in blood. We used HEMS, which could visualize ICG-enhanced structures in vivid color. This system uses a combination of custom-made optical filters and an ultra-high-sensitivity charge-coupled devise (CCD) image sensor with non-Bayer color filter arrays, which can detect visible and NIR rays at 380-1,200 nm without a bias in color balance at 30 frames per second (3, 24). Using this technique, ICG is illuminated with an array of light-emitting diodes at 760 nm, after which the molecule emits light at 830 nm. HEMS then captures the ICG fluorescence images using a color CCD camera (13).

In our study, an additional 7 SLNs were detected by ICG compared to the RI method, all of which were negative for metastasis. In Patients 14 and 16, three and four additional SLNs were identified, respectively. The mean detection time of SLNs biopsy by ICG or the combination of ICG and RI was 19.8 min, while that for SLN biopsy by RI alone was 30.6 min (Table III). The detection time for SLN biopsy by ICG had a tendency to be shorter than that by RI. This suggested that SLN biopsy using ICG or the combination of ICG and RI made it easy for the surgeon to identify SLNs because ICG allowed intraoperative visualization of SLNs by fluorescence. Patient 1, who underwent SLN biopsy using only RI, was diagnosed with a metastatic LN after one year and, thus, underwent neck dissection. On the other hand, patients who underwent SLN biopsy by ICG-only or using combination of ICG and RI were diagnosed with no metastatic LNs. This showed that SLN biopsy by ICG-only or using combination of ICG and RI improved the accuracy of SLN biopsy compared to conventional methods, such as RI alone.

Table I. *Patients' characteristics*.

Patient	Age (years)	Sex	Tumor site	TNM classification
1	61	M	Tongue	T1N0M0
2	79	F	Tongue	T2N0M0
3	67	M	Tongue	T1N0M0
4	55	M	Tongue	T1N0M0
5	59	M	Oropharynx	T2N0M0
6	67	M	Tongue	T2N0M0
7	84	F	Tongue	T2N0M0
8	44	M	Tongue	T2N0M0
9	65	F	Floor of mouth	T1N0M0
10	50	M	Tongue	T1N0M0
11	70	M	Tongue	T2N0M0
12	69	M	Tongue	T2N0M0
13	68	M	Floor of mouth	T1N0M0
14	50	M	Tongue	T2N0M0
15	63	M	Tongue	T2N0M0
16	60	M	Oropharynx	T1N0M0
17	53	M	Tongue	T1N0M0
18	71	F	Hypopharynx	T2N0M0
19	64	M	Hypopharynx	T2N0M0

We were unable to inject the tracer into the hypopharynx or larynx in conscious patients because of the strong laryngeal reflex. We, thus, performed SNL biopsy by ICG alone for Patients 18 and 19, both of whom showed hypopharyngeal primaries. As the ICG method is performed intraoperatively and is unaffected by the laryngeal reflex, these patients could only undergo the ICG method. This suggested that the ICG method could be carried-out without any influence of tumor site. However, some problems remained. In the case of Patient 14, the 3 SLNs identified by ICG-alone might be considered secondary nodes. ICG is a small molecule that binds with albumin (2-3 nm) after administration to show fluorescence (1, 19, 25, 26). The distribution of administered tracer depends on the molecule size, meaning that smaller molecules will be transported quickly (19). Considering this drawback, we performed SLN biopsy using the combination of ICG and RI, when possible. This method was considered to offer a solution to the above drawbacks offering long detection time, quick transportation and improved accuracy of SLN biopsy. In terms of the problem of quick transportation, several studies have recently

Table II. *Numbers of identified SLNs and LN metastasis, and detection time.*

Patients	Total of SLNs	SLNs identified by RI	SLNs identified by ICG	LN metastasis	Method time	Detection (min)	Follow-up time (months)
1	1	1	–	later[a]	RI	30	69.9
2	1	1	–	0	RI	27	62.4
3	1	1	–	0	RI	16	54.5
4	3	3	–	1	RI	34	10.7
5	1	1	–	0	RI	38	21.1
6	4	4	–	0	RI	59	45.0
7	1	1	–	0	RI	24	55.8
8	2	2	–	0	RI	41	58.5
9	2	2	–	0	RI	22	63.3
10	2	2	–	0	RI	20	27.8
11	3	3	–	0	RI	23	59.1
12	3	3	–	0	RI	40	26.1
13	2	2	–	0	RI	24	29.7
14	4	1	4	1	ICG+RI	24	29.1
15	2	2	2	0	ICG+RI	22	25.4
16	4	0	4	0	ICG+RI	41	23.3
17	2	2	2	0	ICG+RI	4	19.2
18	1	-	1	0	ICG	15	29.5
19	2	-	2	0	ICG	13	21.6
Total	41	31		15			

SLN, Sentinel lymph node; RI, radioisotope; ICG, indocyanine green; LN, lymph node. [a]One year later lymphatic metastasis was diagnosed, then neck dissection was performed.

Table III. *Mean detection time of each method.*

Method	ICG or ICG + RI	RI alone
Time (min) (mean±SD)	19.8±12.6	30.6±11.6

ICG, Indocyanine green; RI, radioisotope; SD, standard deviation.

been performed (27, 28). The present study provides a new method for sentinel node navigation surgery, which can also be applied to early laryngeal or pharyngeal cancer. However, the main weakness of this report is the limited number of enrolled patients. We believe that this new method is useful for an optimal visualization of the sentinel node during biopsy. Further studies are warranted to establish ways to better identify SNLs.

Conclusion

SLN biopsy using a combination of ICG and RI is more effective than the conventional method with RI alone. This study suggested that the presented method facilitated identification of SLNs by shortening detection time. However, some problems remain, thus additional studies are required to improve the accuracy of SLN biopsy.

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