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Feasibility of sentinel lymph node detection by near-infrared endoscopy in squamous cell carcinoma of the oral cavity: a pilot study

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Abstract. – OBJECTIVE: Near-Infrared (NIR) fluorescence imaging is a novel technique for intraoperative sentinel lymph node (SLN) identification. It has demonstrated promising results in several surgical specialties. The study aims to evaluate the feasibility of identifying the SLN by indocyanine green (ICG) enhanced NIR endoscopy in squamous cell carcinoma of the oral cavity (OCSCC).

PATIENTS AND METHODS: Seven patients with (cT1-3 N0) OCSCC were included. We injected 1-1.25 ml of ICG (5 mg/ml) at four to five points around the primary. After the elevation of a platysma flap and posterior retraction of the sternocleidomastoid muscle, fluorescence images were taken via IMAGE1 STM NIR/ICG system to define the SLN(s). We sampled fluorescence marked SLN(s) stratified to lymph node levels, followed by level-specified elective neck dissection.

RESULTS: The detection of at least one unilateral or bilateral SLN (range 1-5) was possible in every case. The fluorescence signal occurred, on average, 5.0 ± 2.2 minutes after injection. A total of 22 SLN could be identified. Among 331 histologically examined lymph nodes we could detect one micrometastasis, which was correctly defined as SLN (1/22). There were no false-negative findings. No adverse reactions to ICG occurred.

CONCLUSIONS: Our first results are indicating the concept of SLN concerning OCSCC after the application of real-time NIR fluorescence endoscopy. However, this has to be verified by more extended studies.

Key Words:
Sentinel node biopsy, Oral cavity squamous cell carcinoma, Near-infrared-imaging, Indocyanine green, Neck dissection.

Abbreviations

NIR: Near-Infrared; SLN: Sentinel Lymph Node; ICG: Indocyanine Green; OCSCC: Oral Cavity Squamous Cell Carcinoma; ND: Neck Dissection; SD: Standard Deviation.

Introduction

Squamous cell carcinoma of the oral cavity (OCSCC) frequently metastasizes to cervical lymph nodes, which is the most significant negative prognostic factor[1]. Occult metastases are reported in 20-40% of OCSCC[2,3]. The elective neck dissection (ND) is a frequently performed procedure during surgery in patients with radiologically negative neck (N0) to detect occult metastasis[4]. It seems that 60-80% of patients are overtreated. The increased morbidity and the accompanying impact on the quality of life depend on the extent of dissection[5]. For example, injuries to the accessory nerve and resulting shoulder complaints are reported in 20-67%, depending on the type of ND[6].

Intraoperative mapping of sentinel lymph nodes (SLN) is a promising method to reduce the extent of the ND by facilitating the detection of lymph drainage patterns[7]. Several authors[8] have shown that the incidence of lymphatic metastases is less than 5% in head and neck squamous cell carcinoma if there are no histological findings in SLN. Therefore, SLN mapping is becoming a technique of growing interest in OCSCC, in particular in early stages[9]. Near-Infrared fluorescence (NIR) endoscopy with indocyanine green (ICG) enables real-time intraoperative imaging of the lymphatic tissue with high spatial resolution[10,11]. ICG is a soluble fluorescent dye that can be injected peri-tumoral to facilitate the lymph drainage pattern intraoperatively without significant adverse effects[12,13]. NIR fluorescence imaging has demonstrated promising results in detecting SLN(s) in cervical cancer and melanoma patients[14,15]. There are a few studies[16-19] for head and neck cancer with open systems

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positioned outside the surgical field. The authors confirmed an identification rate of 97-100%, with an average of 3 SLN in each patient, without micro-metastases in non-SLN(s). This study aims to evaluate the feasibility of identifying the SLN in early-stage OCSCC using NIR endoscopy in order to improve the management of the clinical N0 neck.

Patients and Methods

Study Design

This prospective pilot study was conducted at a tertiary hospital and academic cancer center (Department of Otorhinolaryngology, Head and Neck Surgery, University of Erlangen–Nuremberg, Germany). The study was approved by the Local Institutional Ethics Committee (approval number 223_18B) and carried out following the Declaration of Helsinki. Informed consent was obtained from all study participants.

Eligibility Criteria

A total of seven patients with T1-3 OCSCC were included between April 2019 and March 2020. We confirmed malignancy by a biopsy out of the center of the tumor. The clinical neck status was assessed by B-mode sonography and contrast-enhanced computer tomography. None of the patients had evidence for the presence of lymphatic metastasis (cN0). The therapy decision was made in our interdisciplinary tumor board and carried out according to the current guidelines. We obtained informed consent before participation in the study. Exclusion criteria were prior treatment of any head and neck cancer, presence of distant metastasis, state after prior surgery or radiotherapy in the head and neck area, pregnancy, thyroid dysfunction, severe kidney failure, and allergy to ICG or iodine. Our and international treatment standards were not altered or influenced in any way by the use of ICG for sentinel node mapping and by the lymph node harvesting procedure itself.

Technical Details

We performed intraoperative imaging using an IMAGE1 S™ NIR/ICG (KARL STORZ SE & Co.KG, Tuttlingen, Germany). The system included a full high definition camera (IMAGE1 S H3-Z FI) connected to a 0° HOPKINS ICG telescope with a 10 mm diameter equipped with a specific filter for the detection of near-infrared imaging of ICG. The cold light fountain D-Light P provides visible and near-infrared excitation light. The surgeon can switch between both options by either a footswitch panel or via the camera head buttons. We used ICG as an optical imaging agent. ICG molecules absorb light in 690-830 nm wavelength range and emit fluorescence in 750-875 nm range, with its peak emission around 825 nm[13].

Surgical Procedure and Intraoperative Imaging

All NDs and the SLN procedure were performed by two experienced surgeons of our department in a standardized manner. To analyze the exact distribution of the ICG, we exposed the soft tissue of the neck before starting imaging. For this purpose, we prepared a subplatysmal skin flap and inserted retractors between the digastric-, omohyoid- and sternocleidomastoid muscles according to a standardized protocol (Figure 1). Subsequently, 1-1.25 ml (in a concentration of 5 mg/ml) of ICG (VERDYE, Diagnostic Green, Aschheim-Dornach, Germany) was injected submucously at four to five points around the primary. The NIR-endoscope (HOPKINS Optik 0°, NIR/ICG, Ø 10 mm, KARL STORZ SE & Co. KG, Tuttlingen, Germany) was positioned above the surgical field (Figure 1). During the imaging procedure, the endoscope was rotated into the operating field to reduce the distance and thus to increase signal detection. Each lymph node with a bright fluorescent signal was defined as SLN and marked by sutures (Figure 2). The time until registration of the fluorescence enhancement was measured. We could identify further SLN(s) of different tiers based on the time sequence of fluorescence enhancement. The lymph drainage pattern was noted, and SLN(s) were sampled in a level-specific manner. We were able to distinguish fluorescent lymph nodes from vessels or artificial marked non-lymphatic tissue (Figures 2 and 3). After completion of the SLN procedure, the primary tumor was resected. Subsequently, we performed an elective ND, including levels I-IV, according to the American Head and Neck Society, as a standard of reference[20]. We provided accurate detection of SLN-negative occult metastases by separate dissection of each level. The entire neck specimen and the separately dissected SLN(s) were processed by hematoxylin-eosin staining on 2 µm whole slide sections by experienced colleagues of the Institute of Pathology at the University of Erlangen, following a standard protocol.

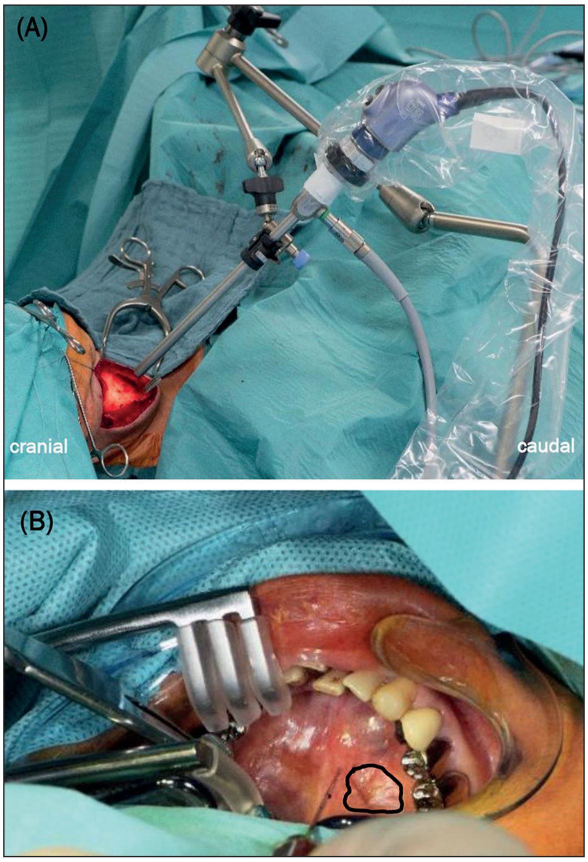

Figure 1. Intraoperative setup before SLN mapping in a case of T1N0 carcinoma of the anterior oral floor (G2, Infiltration depth 5 mm): **(A)** Exposure of the soft tissue of the neck (on the right side) and positioning of the NIR endoscope (HOPKINS Optics 0°, NIR/ICG, Ø 10 mm, Karl Storz, Tuttlingen, Germany). **(B)** One milliliter of ICG at a concentration of 5 mg/ml is injected at four points around the tumor (encircled area).

Outcome Parameters

The aim of this pilot study refers to the proof of concept. The primary endpoints were the identification rate of the SLN(s) and the spatial and temporal distribution of ICG. Secondary endpoints were the rate of false negative and true positive lymph nodes.

Statistical Analysis

Patients' and tumor characteristics, as well as time values and dimensions applied, are presented in mean and standard deviation. We also presented the total number of all SLN and resected lymph nodes with mean and standard deviation. The frequencies and distribution of SLN and non-SLN lymph nodes are presented in relative and absolute values (%; n/n). Statistical analysis was performed using SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics and Oncological Findings

Patient and tumor characteristics are presented in Table I. Seven patients with (T1-3) OCSCC and clinical N0 neck were included in this study. In three cases, the tumor was located in the anterior oral floor. In four cases, the tumor was located in the lateral tongue. The average size of the primary was 1.7 ± 1.3 cm. The average infiltration depth was 7 ± 6.2 mm. All patients underwent a

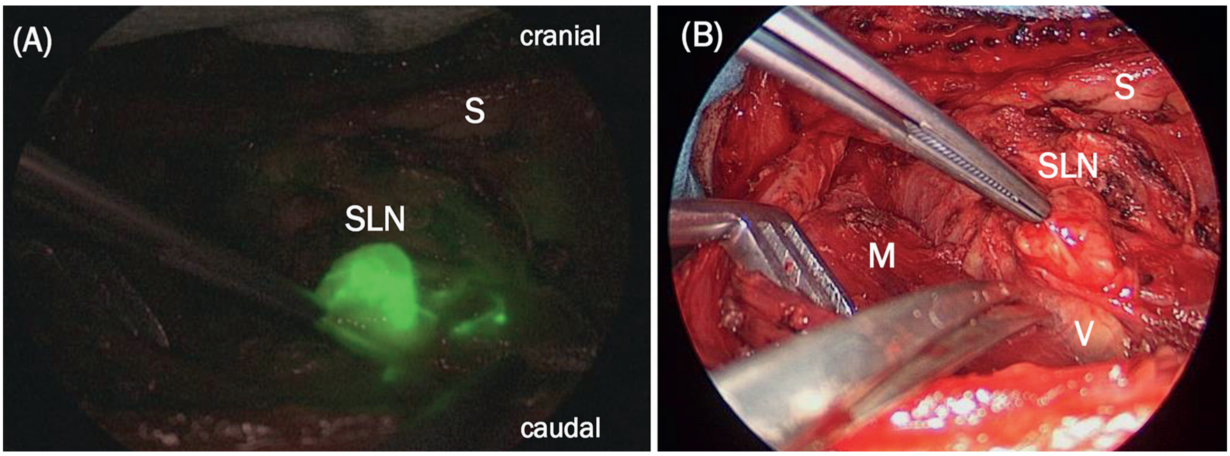

Figure 2. Sentinel node mapping using NIR endoscopy in a T3N0 carcinoma of the tongue (G3, Infiltration depth 15 mm): **(A)** Intraoperative findings in near-infrared mode (right side of the neck) 4 minutes after injection of ICG (working distance 5 cm): a fluorescent lymph node in level III is defined as sentinel lymph node (SLN). Besides, the draining lymph vessels are visible by a slight accumulation of ICG. **(B)** The internal jugular vein (V) is visible in color mode. ICG is not circulating in the venous system. S = submandibular gland; M = sternocleidomastoid muscle.

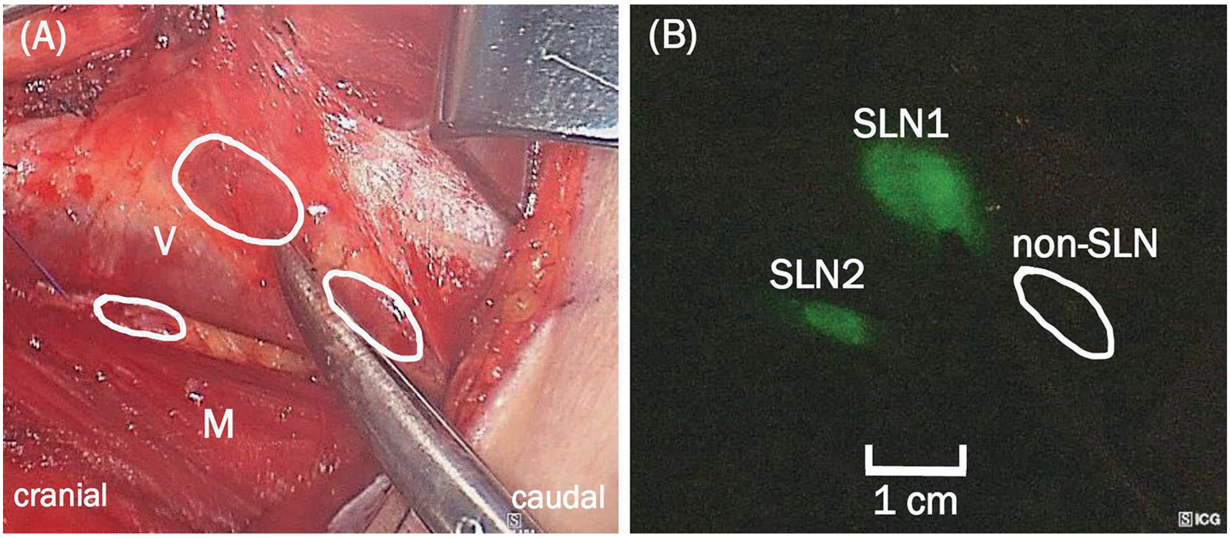

Figure 3. Identification of higher tier lymph nodes in a T1N0 carcinoma of the tongue (G2, Infiltration depth 2 mm): **(A)** Illustrated is the soft tissues along the internal jugular vein (V) of the right site (working distance 35 cm). Various lymph nodes can be recognized (circles). **(B)** In NIR endoscopy, two lymph nodes are defined as sentinel lymph nodes (SLN 1&2) due to fluorescent enhancement. Nearby, a non-SLN. The visualization of the SLN in near-infrared mode shows a sharp selectivity with minimal scattering effects. SLN 2 was identified at a depth of 1.5 cm beyond the internal jugular vein (V); M = sternocleidomastoid muscle.

radical resection of the primary tumor with negative surgical margins. Three patients received a transoral approach, and four patients received a combined approach with a reconstruction of the defect. We performed a unilateral ND (level I-IV) in two cases and a bilateral ND (level I-IV) in five cases (Table I and II).

Intraoperative Lymph Node Detection and Histological Findings

After the application of ICG, the first fluorescence signal occurred on average after 5.0 ± 2.2 minutes (mean ± SD). We detected additional fluorescence enhancement on average after 7.2 ± 3.3 minutes (SLN 2), 13.4 ± 8.4 minutes (SLN 3), 18.0 ± 11.0 minutes (SLN 4), and 20.0 minutes (SLN 5) (Table III). Each SLN measured more than one centimeter in its largest diameter (Table II). Additionally, there was no intravascular distribution of ICG (Figure 2). The fluorescence imaging added an average of not more than 20 minutes to the total operation time compared with a standard ND procedure (in the study setting). We did not observe adverse reactions.

In every case (n = 7), NIR fluorescence imaging enabled the identification of one or more SLN (range 1-5). In total, we detected 22 SLNs, and a total of 331 lymph nodes were harvested (range 24-84). On average, 3.1 ± 1.3 SLN(s) were identified, and a total of 47.3 ± 19,4 lymph nodes were

Table I. Patient and tumor characteristics.

Patient no.	Age (years)	Localization of primary	T-stage	Tumor size (cm)∞	Infiltration depth (mm)	Grading	Type of surgery
1.	59	Oral floor	1	0.2	5	G2	TOA
2.	87	Tongue	2	2.5	4	G2	TOA
3.	56	Oral floor	1	1.2	4	G3	CA
4.	54	Oral floor	3	2.6	15	G3	CA
5	58	Tongue	1	1.2	2	G2	TOA
6.	54	Tongue	3	3.5	17	G3	CA
7.	49	Tongue	1	0.3	2	G2	CA

Abbreviations: ∞ in largest diameter; TOA = Transoral Approach, CA = Combined Approach.

Table II. Intraoperative SLN mapping.

Patient no.	NIR hotspots	Level of SLNα	Time to ICG uptake (min)	SLN size (cm)¥	LN(s) harvested	ND	LN(+)
1.	3	IIA, IIB∞, IB	9; 10; 12	1.2; 1.5; 1.3	57	Bilat	No
2.	1	IIA	4	1.8	24	Unilat	No
3.	2	IIB, III	5; 7	1.0; 2.3	44	Bilat	No
4.	3	III, IIA∞, IIA	4; 5; 7	1.3; 1.2; 1.4	46	Bilat	No
5.	4	IIA, IIB, IV, III	2; 3; 5; 7	1.9; 1.9; 1.5; 1.0	31	Unilat	No
6.	5	IIA, IIA∞, III, III∞, IV	5; 6; 17; 18; 20	1.0; 1.0; 2.5; 2:0, 1:0	45	Bbilat	IIA
7.	4	IIA, III, III∞, IV	6; 12; 20; 20	1.5; 2.1; 2.1; 1.0	84	Bilat	No

Abbreviations: NIR = Near-Infrared; SLN = Sentinel Lymph Node; ICG = Indocyanine Green; SD = Standard Deviation; LN = Lymph Node; ND = Neck Dissection; LN(+) = Micro-Metastasis; α SLN 1-4 according to the detection time; ∞ located in contralateral neck; ¥ in largest diameter.

resected in each patient (Table II). The anatomical distribution of these 22 SLNs in relation to the resected lymph nodes in each basin was as follows: IIA 16.7 (8/48), III 6.9% (7/102), IIB 4.9% (3/61), IV 4.5% (3/66), IB 2.8% (1/35), and level IA 0% (0/19). Histopathologically, we confirmed a micrometastasis in the ipsilateral level IIA (Patient No. 6). The location of the SNL concerning the primary tumor is presented in Tables I and II.

Discussion

To our knowledge, this study is the first evaluating the IMAGE1 S™ NIR/ICG imaging system for intraoperative real-time NIR endoscopy in OCSCC. We identified at least one SLN in each case. The SLN(s) appeared as bright fluorescent spots, on average, 5.0 ± 2.2 minutes after injection of ICG. Anatomic distribution of the SLN(s) was similar to the metastatic pattern of oral cancer, with the majority of metastases in level I, II and III[21]. Regarding the tumor localization, carcinomas of the oral floor are mainly associated with metastasis in level I, II, and III, whereas carcinomas of the tongue show additional metastases in level IV. Metastases in level V are rare[22,23]. In accordance, we detected the SLN in level I to III in patients with carcinomas of the oral floor (patient no. 1, 3, and 4). In three out of four patients with carcinoma of the tongue (patient no. 5, 6, and 7), SLNs in level IV were additionally detected.

The identification of SLN in the head and neck area is still controversial, although it attracted more interest in the clinical N0 neck situation of OCSCC. It provides the identification of the first drainage lymph node, which supposably is carrying the highest risk of being affected in the case of metastatic disease[24]. After identification, a frozen section can be performed. In the case of micro-metastatic spread, a complete ND is indicated[25]. In the absence of malignancy, the ND may be abandoned. This strategy has the potential to enable a de-escalation of surgical therapy without compromising oncological results[24]. Several methods have been described for SLN identification. The frequently used lymphoscintigraphy with ^{99m}technetium demonstrated an identification rate of 86-95% with a false-negative rate of 2-3%[4,8,26]. It is characterized by high

Table III. Characteristics of SLN.

SLN no.	Level of SLN	Time to ICG uptake (min) Mean ± SD	SLN size (cm)¥ Mean ± SD
SLN 1 (n = 7)	IIA (n = 4); IIB, III (n = 2)	5.0 ± 2.2	1.4 ± 0.4
SLN 2 (n = 6)	IIA (n = 2); IIB (n = 2); III (n = 2)	7.2 ± 3.3	1.7 ± 0.5
SLN 3 (n = 5)	IB, IIA (n = 2); III; IV	13.4 ± 8.4	1.8 ± 0.5
SLN 4 (n = 3)	III (n = 2); IV	18.0 ± 11.0	1.3 ± 0.6
SLN 5 (n = 1)	IV	20	1.0

Abbreviations: SLN = Sentinel Lymph Node; ICG = Indocyanine Green; SD = Standard Deviation; ¥ in largest diameter.

tissue penetration. A drawback is the limited spatial resolution, which may affect the accuracy of the intraoperative navigation, especially if the SLN is located close to the injection site[17]. The lack of evidence of a survival benefit of SLN mapping compared to ND in prospective controlled trials may be one reason why this technique currently is established only in a few centers.

The use of ICG for the detection of SLN successfully was introduced by Kitai et al[27] in 2005 in patients with breast cancer. There are several advantages of fluorescent imaging compared to radioactive tracers. The radiation-free, fluorescent dye has been in clinical use for decades and can be considered very safe, with a low rate of adverse effects[12,13]. Furthermore, no special radiation protection is required. The costs of ICG is much lower than for a radiotracer. Besides this, the fluorescence imaging system is less expensive than a radiation detection probe[18]. Image acquisition can be performed mono-institutional by the treating surgeon. There are a few studies[16-19] that report on ICG guided SLN mapping in patients with squamous cell carcinoma of the oropharynx and oral cavity. All authors referred good feasibility with an identification rate of 97-100%. Limitations have been described in the low tissue penetration depth of 0.5–1 cm using open imaging systems, which are positioned above the surgical field[16]. The lymph drainage of the oral cavity and the oropharynx runs in deep fatty tissue and can be covered either by the mandible or the sternocleidomastoid muscle. A skin incision, retraction of the muscles, and subplatysmal exposure of the soft tissue are therefore currently essential[18].

The IMAGE1 S™ NIR/ICG is a laparoscopic imaging system. The telescope has a shorter working distance compared to an open system, and this results in an improved near-infrared image and a higher penetration depth. A dynamic examination in the surgical field could improve the SLN procedure, especially in the submandibular region. By using a holding device, the surgeon can fix the endoscope in different positions during surgery and simultaneously dissect the SLN. Besides, the endoscopic technique offers the possibility to reduce surgical access. The cervical lymph nodes are typically located in close anatomical proximity to each other. With the current system, we achieved a differentiation of single lymph nodes and the distinction between SLN and non-SLN with minimal scattering effects (Figure 3). We were also able to identify lymph nodes at a depth of about 1.5-2 cm embedded in fatty tissue. After a rapid distribution through the draining lymph vessels, we observed the fluorescence enhancement in additional lymph nodes (SLN 2-5) with increasing observation time (Table III). This underlines the relevance of the time-related identification of the SLN in an intraoperative setting. As a result, the intraoperative injection of ICG may prevent a false identification of higher tier nodes. If the time dependence of the ICG distribution is not considered adequately, a subgroup of lymph nodes of higher tiers may be marked and falsely identified as SLN. However, it must also be taken into account that in the case of multiple drainage patterns, several relevant SLNs can also be present.

We can confirm the secure and straightforward feasibility and real-time measurement of lymphatic drainage patterns with the IMAGE1 S™ NIR/ICG imaging system. Although ICG application and examination takes around 20 minutes, operating time may be reduced if the SLN is negative, since a complete ND would not be needed.

The scope of this evaluation refers only to an analysis of feasibility. There was no case of neck metastasis when SLN was negative, which suggests a low false-negative rate. In order to evaluate the accuracy of this method, a higher case number is necessary to determine the false-negative rate and the negative-predictive value. The purpose of continuing this study to a more significant case number is to evaluate if the removal of the SLN alone could reliably demonstrate the cervical nodal status for OCSCC. Future research should, therefore, be focused on the timely association and distribution of the fluorescent tracer and the occurrence and distribution of occult metastasis. The further development of this technology is in prospect in order to reduce the incision or to enable transcutaneous utilization.

Conclusions

This study shows the feasibility of detecting draining lymph nodes in OCSCC patients using NIR endoscopy in a real-time, intraoperative setting. If this method proves to be reliable in further studies, including higher numbers of patients, it has the potential to reduce the invasiveness of surgical therapy in patients with cN0 oral carcinoma.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

KARL STORZ SE & Co.KG (Tuttlingen, Germany) provided the imaging system to examination without influence on the study protocol, and no financial contribution.

Ethical Approval

All procedures performed in this study involving human participants were following the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval (approval number 223_18B) was given by the Clinical Research Ethics Committee of the Medical Faculty (Friedrich Alexander University of Erlangen-Nuremberg, Germany).

Informed Consent

Informed consent was obtained from all study participants.

Authors' Contribution

The Authors declare that they have no conflict of interests.

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