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Jacobs Journal of Otolaryngology

Editorial Article

Impact of Near-Infrared Indocyanine Green Fluorescent Image on Minimally Invasive Treatments for Head and Neck Cancer

Junkichi Yokoyama[1,2*], Kenichiro Ishibasi[1]

[1]*Department of Otolaryngology Head and Neck Surgery, Moriyama Memorial Hospital*

[2]*Department of Otolaryngology Head and Neck Surgery, Juntendo University, School of Medicine*

**Corresponding author: Dr. Junkichi Yokoyama, Department of Otolaryngology Head and NeckSurgery, Moriyama Memorial Hospital, 7-12-7 Nishikasai, Edogawa-ku, Tokyo, Japan, Tel: +81-3-5679-1211; Fax: +81-5679-1212; Email: jyokoya@juntendo.ac.jp*

Received: 03-06-2016

Accepted: 03-07-2016

Published: 04-20-2016

Keywords: ICG (Indocyanine Green); Fluorescence Imaging; Sentinel Lymph Node (SLN); Head And Neck Cancer; Lymphatic Chemotherapy; Intra-Arterial Chemotherapy

Indocyanine green

Indocyanine green (ICG) is a water soluble, tricarbocyanine dye widely employed in medical applications. After FDA approval in 1959, ICG was initially used primarily in hepatic function diagnosis. With a molecular weight of 775, ICG has a peak spectral absorption of approximately 800 nm. Near infrared frequencies penetrate retinal layers allowing ICG angiography to image patterns of circulation. Since the 1980s, the development of advanced cameras has significantly reduced the technical difficulties associated with ICG imaging. More than 3,000 scientific papers on ICG have now been published worldwide [1].

In the following we discuss ICG fluorescence imaging technics for the treatment of head and neck cancer in order to minimalize procedure invasiveness and reduce potential complications.

Sentinel Lymph Node(SLN) Navigation Surgery

The sentinel lymph node (SLN) is thought to be the foremost possible micrometastatic site via lymphatic drainage from the primary cancer [2]. Neck lymph node metastasis is the most significant prognostic factor of head and neck cancer however, there remains debate as to the most effectivetreatment of clinical N0 neck metastasis. SLN navigation surgery decreases morbidity associated with neck dissection and reduces the potential of recurrence. While radiocolloids have previously been used to detect SLN, there are disadvantages including the lack of real-time intraoperative visual information and the phenomena of "shine-through" radioactivity due to scattering from the primary site. This is particularly evident in cases related to the floor of the mouth. To negotiate these problems, ICG fluorescence imaging has been used for the detection of SLN when dealing with cases of oral cancer. The advantages of ICG fluorescence imaging include access to real-time intraoperative visual information and only minor effects of "shine-through" even in cases related to the floor of the mouth.

ICG Fluorescence Imaging-Guide Surgery For Parapharyngeal Space Tumors

In the narrow parapharyngeal space, it is exceedingly difficult to resect tumors without complications such as dysphagia and carotid artery rupture [3]. In order to minimize surgical complications and preserve organs, endoscopic, or robotic surgery is often executed when performing head and neck surgery. We have applied ICG florescence imaging methods for navigation surgery and have demonstrated the advantages and effectiveness of ICG fluorescent image-guided surgery for the safe resection of parapharyngeal space tumors [4].

All tumors displayed bright fluorescence emissions which clearly contrasted with the surrounding normal structures. Even in cases when the submucosal tumor was covered with

and obscured by fascia, we could observe the tumor clearly. Tumors located behind the carotid artery and lower cranial nerves also displayed bright fluorescence emissions and could therefore be clearly detected. Accordingly, we could remove the tumor safely and noninvasively which enabled the successful preservation of pharyngeal functions.

The application of endoscopic and robotic surgery for the parapharyngeal space lesions enables surgeons to perform minimally invasive surgery with superior results. However, we need to be able to detect parapharyngeal tumors in deeper and invisible areas particularly when palpation is not possible. This is required in order to resect tumors safely and can be significantly aided through effective tumor detection carried out with ICG fluorescent imaging.

Lymphatic Chemotherapy For Head and Neck Cancer

According to the Sentinel theory, metastatic lymph nodes are directly connected with primary tumors via lymphatic canals. Lymphatic chemotherapy is defined as chemotherapy using lymphatic canals between metastatic lymph nodes and primary tumors. This therapy is viewed as an ultimate cancer treatment which is both highly effective and noninvasive.

Clinical No Cases (Occult Neck Metastasis)

We have implemented a newly developed lymphatic chemotherapy procedure targeting the SLN using intra-arterial (I-A) chemotherapy for oral cancer in order to improve prognosis and to preserve organs while avoiding surgical complications [5]. Our procedure for lymphatic chemotherapy employs an anti-cancer drug administered to the primary cancer which then moves selectively to SLNs via lymphatic canals. As a result, the anti-cancer drug is accumulated in the SLNs and results in a higher anti-cancer drug concentration in the SLNs than non-SLNs. We have adopted I-A chemotherapy administered to the primary cancer so as to increase the CDDP concentration. To examine the potential advantages, we compared the CDDP concentration of SLNs with that of non-SLNs. The mean CDDP concentrations in the SLNs and non-SLNs were 1.2μg/g and 0.35μg/g, respectively ($p<0.05$). Our ICG fluorescence procedure clearly revealed that all metastatic lymph nodes, including SLNs, were without false negative SLNs.

Clinical Neck Metastasis Cases

Modified radical neck dissection can be the cause of severe postoperative complications. Instead of neck dissection and the associated surgical complications, minimally invasive lymphatic chemotherapy targeting neck metastasis based on the sentinel concept may contribute to the development of a revolutionary cancer treatment. This could potentially provide a superior method for the treatment of head and neck cancer which has been a key objective for researchers over many years. We consider I-A chemotherapy administered to primary oral cancers as not only organ preservation therapy, but also a newly developed lymphatic chemotherapy targeting neck metastasis in order to improve prognosis. We have evaluated the effect of lymphatic chemotherapy targeting neck metastases in patients with oral cancer (T3N2bM0) by measuring CDDP concentrations in metastatic lymph nodes and pathological effects [6].

The mean CDDP concentrations in the metastatic lymph nodes and non-SLNs were 2.35 μg/g and 1.08 μg/g, respectively ($p = 0.034$). Of 27 metastatic nodes, 24 (89%) were identified by ICG fluorescence imaging; however, only 18 (67%) were identified by the conventional method ($p = 0.043$).

Large metastatic cancers were significantly reduced is size and resulted in scar tissue. Apoptosis was detected in all 27 metastatic lymph nodes and positive results were recognized pathologically. Our I-A chemotherapy is expected to contribute not only to primary organ preservation but also to positive prognosis by controlling the metastatic lymph nodes. Of importance is that the ICG fluorescence imaging procedure demonstrated higher success rates for the detection of SLNs in patients with tumors located in the tongue than the radioactivity method.

Perfusion Diagnostics of Reconstructive Flap

When advanced head and neck cancer are removed, a vascularized reconstructive flap is required. It is difficult to observe perfusion diagnostics of the grafted reconstructive flap in the pharynx or skull base. ICG fluorescence image is applied as a marker in the assessment of the perfusion of the reconstructive flap during intraoperative or postoperative days. The ICG fluorescence imaging effectively reveals the blood supply to the grafted flap in real time [7].

Contribution to Superselective Intra-Arterial(I-A) Chemotherapy for Advanced Head and Neck Cancer

For advanced paranasal sinus cancer, which is resistant to conventional systemic chemotherapy, superselective I-A chemotherapy is believed to increase the concentration of anti-cancer drugs in the tumor. It is most important for I-A chemotherapy to obtain precise information about the blood supply to tumors in order to prevent recurrence. We conducted CT angiography in order to accurately determine the blood supply to tumors in cases of head and neck cancer [8]. However, it is problematic confirming the drug distribution areas when the tumor is superficially invasive or the patient has undergone dental treatment involving metal fillings. To overcome the disadvantages of CT-angiography, ICG fluorescence imaging has been applied for evaluation of tumor blood supplies.

ICG fluorescence imaging combined with I-A chemotherapy

compensated for the deficiencies of CT angiography for paranasal sinus cancer. ICG fluorescence provided greater clarity and more constructive information concerning the feeders to cancers [9, 10]

In conclusion, as ICG fluorescence imaging for head and neck cancer visualizes blood vessels and lymphatic canals, it is possible to detect primary lesions or lymphatic metastasis without invasiveness. Noninvasive treatment for head and neck cancer can be conducted effectively and safely.

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