



# Oxygen saturation imaging as a useful tool for visualizing the mode of action of photodynamic therapy for esophageal cancer

Masayuki Suyama, MD, PhD, Yusuke Yoda, MD, Yoichi Yamamoto, MD, PhD, Hironori Sunakawa, MD, Tatsunori Minamide, MD, Keisuke Hori, MD, PhD, Hiroaki Ikematsu, MD, PhD, Tomonori Yano, MD, PhD

**Background and aims:** Oxygen saturation (OS) imaging is a novel technique that directly measures and visualizes the tissue oxygen saturation at the surface of the GI tract. Our purpose was to evaluate the ability of OS imaging to visualize the action mode of photodynamic therapy (PDT).

**Methods:** Eight patients with local recurrence after chemoradiotherapy for esophageal cancer were enrolled. OS imaging observation was performed before PDT, after 100 J/cm<sup>2</sup> illumination and illumination completion, and on the second day.

**Results:** OS imaging showed an extreme change in the hypoxic state in the illuminated area, although the change was near invisible on white-light imaging. The median tissue oxygen saturation value at the tumor lesion was 61.5% (range, 36%-91%) before PDT and significantly decreased immediately after illumination: 11% (range, 0%-57%) after 100 J/cm<sup>2</sup> illumination, 1% (range, 0%-6%) at PDT completion, and 2% (range, 0%-12%) on the second day.

**Conclusions:** OS imaging could be a useful tool to visualize changes after PDT. (VideoGIE 2020;5:496-9.)

Photodynamic therapy (PDT) is one modality of multidisciplinary treatment for cancer, such as curative salvage alternatives for local failure after chemoradiotherapy or radiotherapy in patients with esophageal cancer.<sup>1-3</sup> PDT is an endoscopic cancer treatment modality consisting of a photosensitizer and involves specific-wavelength laser light illumination. PDT produces reactive oxygen species in cancer cells and induces the vascular shutdown effect.<sup>4,5</sup>

The mode of action of PDT cannot be visualized by ordinary white-light imaging (WLI) endoscopy in clinical practice. Changes in the laser-illuminated area are very minor immediately after illumination and on the day after PDT. Therefore, it is difficult to determine whether the illuminated area is adequate during or after the PDT procedure.

Oxygen saturation (OS) imaging is a novel endoscopic technique that can directly measure and visualize the tissue oxygen saturation (StO<sub>2</sub>) of the GI tract surface.<sup>6</sup> The system uses 2 laser light wavelengths (445 and 473 nm) to detect spectral differences between oxyhemoglobin and deoxyhemoglobin. The mucosal surface is alternately illuminated at these 2 wavelengths, and the reflected light is sequentially detected with a color charge-coupled device in synchronization with light switching. The obtained images are processed and transformed into an StO<sub>2</sub> pseudocolor map. This endoscopy system can simultaneously project 2 images (ie, white-light and pseudocolor mapping images) for StO<sub>2</sub> value determination. The scale of the color layer is used, and the unit area is displayed

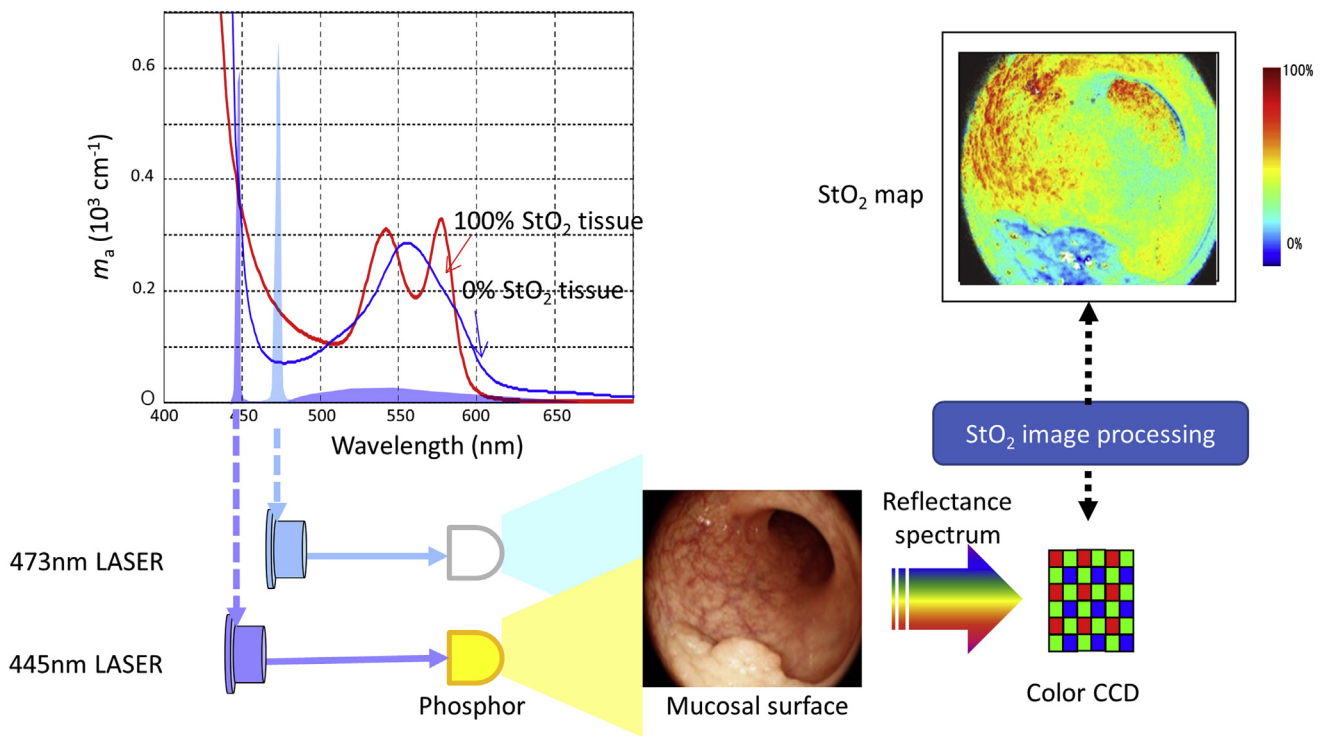
in red and blue as the StO<sub>2</sub> value increases and decreases, respectively (Fig. 1 and Video 1, available online at [www.VideoGIE.org](http://www.VideoGIE.org)). Subsequently, the StO<sub>2</sub> value of a certain area in the obtained image can be calculated from the color data.

OS imaging is theoretically an ideal modality for observation of the PDT-induced vascular shutdown effect. The purpose of this study was to validate the ability of OS imaging to visualize the mode of action of PDT in esophageal cancer.

## METHODS

Consecutive patients with local recurrence after chemoradiotherapy for esophageal cancer who received PDT and were evaluated with the OS imaging endoscopy system (FUJIFILM, Co, Tokyo, Japan) were enrolled between August and October 2018. This study was approved by the Institutional Review Board of the National Cancer Center of Japan and was conducted in accordance with the tenets of the Declaration of Helsinki (approval number: 2017-434).

The procedure of PDT commenced with intravenous administration of talaporfin sodium (Leserphyrin; Meiji-Seika Pharma, Tokyo, Japan) followed by 664-nm wavelength diode laser illumination. The fluence of the laser was set at 100 J/cm<sup>2</sup> with a fluence rate of 150 mW/cm<sup>2</sup>.



**Figure 1.** Schematic illustration of oxygen saturation imaging. The 445-nm laser and the 473-nm laser light alternately illuminated the mucosal surface, and the reflected lights were sequentially detected with a color charge-coupled device (CCD). The obtained images were processed and transformed into a superficial tissue oxygen saturation (StO<sub>2</sub>) map.

If the lesions were larger than 1 cm<sup>2</sup>, additional laser illumination was performed and overlapped to cover the whole lesion.<sup>1</sup>

Observation with the OS imaging endoscopy system was performed before illumination, after illumination of 100 J/cm<sup>2</sup>, after illumination completion, and 1 day after PDT. Subsequently, the obtained image was used to measure the StO<sub>2</sub> values at 3 points (ie, at the center and at both ends of the lesion).

**RESULTS**

Eight patients underwent PDT during the study period. All patients were male, and the lesions were cT1a or cT1b (patient and lesion characteristics are summarized in Table 1).

Figure 2A shows the changes in WLI and OS imaging before and after PDT illumination. OS imaging showed an extreme change to the hypoxic state of the illuminated area after illumination at 100 J/cm<sup>2</sup>, although the change was invisible on WLI. After completion of the illumination, the lesion area was covered in blue color. On day 2, we confirmed that hypoxia was maintained using OS imaging. On day 7, the laser-illuminated area showed ulcers in all cases.

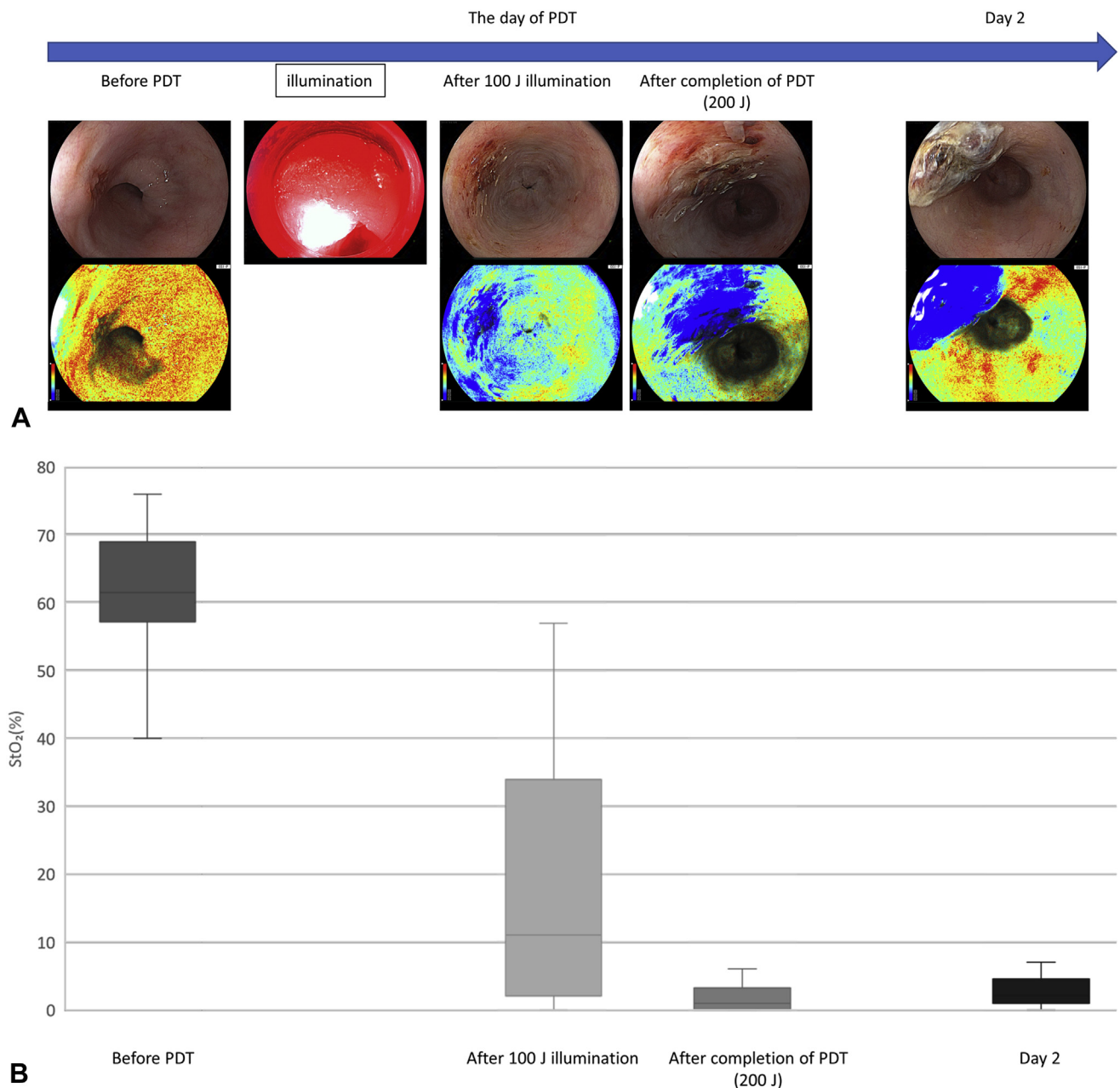
The StO<sub>2</sub> results obtained from OS imaging are displayed in Figure 2B. Before PDT, the median StO<sub>2</sub> value was 61.5%

**TABLE 1. Patient and lesion characteristics**

| N = 8                                 |              |
|---------------------------------------|--------------|
| <b>Patient characteristics</b>        |              |
| <b>Sex, male/female</b>               | 8/0          |
| <b>Median age, (range), y</b>         | 80.5 (60-85) |
| <b>Lesion characteristics</b>         |              |
| <b>Tumor location</b>                 |              |
| <b>Upper/middle/lower</b>             | 0/6/2        |
| <b>T stage</b>                        |              |
| <b>cT1a/cT1b/cT2</b>                  | 3/5/0        |
| <b>Histopathology</b>                 |              |
| <b>Squamous cell carcinoma/others</b> | 8/0          |

(range, 36%-91%). After laser illumination at 100 J/cm<sup>2</sup>, the median StO<sub>2</sub> value significantly decreased as the laser dose increased and was 11% (range, 0%-57%) after 100 J/cm<sup>2</sup> laser illumination and 1% (range, 0%-6%) at PDT completion. On day 2, the laser-illuminated area corresponded to the ischemic mucosa on WLI, and the hypoxic state could be confirmed on OS imaging; the median StO<sub>2</sub> value was 2% (range, 0%-12%).

Five patients achieved local complete response. Local recurrence after PDT was observed in 3 patients during a median follow-up period of 1.5 months (range, 1-7 months).



**Figure 2.** **A**, WLI and OS imaging before and after PDT. In the OS imaging observation, the illuminated site changes to a hypoxic region immediately after PDT and is displayed in *blue*. **B**, StO<sub>2</sub> value at the tumor lesion before and after PDT. WLI, White-light imaging; OS, oxygen saturation; PDT, photodynamic therapy; StO<sub>2</sub> tissue oxygen saturation.

## DISCUSSION

To our knowledge, this is the first clinical report to use OS imaging for real-time monitoring during PDT. We were able to obtain endoscopic images that displayed dramatic changes in hypoxic status immediately after PDT illumination.

Endoscopic PDT is one of the curative salvage alternatives for local failure after chemoradiotherapy or radiotherapy in patients with esophageal cancer.<sup>1-3</sup> Despite the effectiveness of the treatment, it is difficult to determine whether the lighting is adequate using WLI. In this

study, the use of OS imaging allowed real-time visualization and confirmation of the illuminated area.

PDT uses nontoxic photosensitizers and harmless visible light in combination with oxygen to produce cytotoxic reactive oxygen species,<sup>7</sup> which can destroy tumors through multifactorial mechanisms. PDT can directly affect cancer cells by inducing necrosis and/or apoptosis in the tumoral vasculature.<sup>8</sup> Some investigators have demonstrated the mode of action of PDT using functional magnetic resonance imaging<sup>9</sup> or optoacoustic imaging<sup>10</sup> in animal models. We would have clinically demonstrated the mode of action of

PDT through the decreasing StO<sub>2</sub> levels after treatment in OS imaging.

The efficacy of PDT is influenced by the lesions' characteristics, including tumor depth or histology, as well as the adequate laser illumination. In this study, 3 of 8 patients developed local recurrence approximately 2 months after PDT despite sufficient change being noted on OS imaging. In addition, the efficacy of PDT in the present study was lower compared with our previous report, despite similar background and characteristics.<sup>1</sup> The reason for this relatively low complete response rate was not clear because of the small number of cases. Between patients with local recurrence and without recurrence, there was not a significant difference in the saturation level after PDT completion and at 2 days. Therefore, OS imaging could be a useful tool to confirm the area of illumination, but it is not yet known whether findings of OS imaging can predict the efficacy of PDT.

The limitation of this study is a small number of cases. It is necessary to evaluate the relation between the efficacy of PDT and findings of OS imaging with further cases.

To conclude, OS imaging can visualize the changes in StO<sub>2</sub> levels in tumors before and after laser illumination and can be considered a clinically useful endoscopic functional imaging that can visualize the mode of action of PDT in real time.

## ACKNOWLEDGMENTS

A part of this study was supported by the National Cancer Center Research and Development Fund (29-A-10) of Japan. This lists individuals who have made important contributions without meeting authorship criteria. We thank all the patients, their families, the clinicians at this center, and the investigators who participated in this study. Technical support for medical devices was provided by T. Omori, T. Saito, K. Otani, Y. Yoshimori, N. Shigeta, T. Okamoto, and S. Ozawa of Fujifilm Corporation, Tokyo, Japan.

## DISCLOSURES

*Dr Yano receives research grant funding from Fujifilm. All other authors disclosed no financial relation-*

*ships. OS imaging endoscopy system was provided by Fujifilm Corporation, Tokyo, Japan.*

*Abbreviations: OS, oxygen saturation; PDT, photodynamic therapy; StO<sub>2</sub>, tissue oxygen saturation; WLI, white-light imaging.*

## REFERENCES

1. Yano T, Kasai H, Horimatsu T, et al. A multicenter phase II study of salvage photodynamic therapy using talaporfin sodium (ME2906) and a diode laser (PNL6405EPG) for local failure after chemoradiotherapy or radiotherapy for esophageal cancer. *Oncotarget* 2017;8: 22135-44.
2. Hatogai K, Yano T, Kojima T, et al. Local efficacy and survival outcome of salvage endoscopic therapy for local recurrent lesions after definitive chemoradiotherapy for esophageal cancer. *Radiat Oncol* 2016;11:31.
3. Minamide T, Yoda Y, Hori K, et al. Advantages of salvage photodynamic therapy using talaporfin sodium for local failure after chemoradiotherapy or radiotherapy for esophageal cancer. *Surg Endosc* 2020;34:899-906.
4. Dolmans DE, Kadambi A, Hill JS, et al. Vascular accumulation of a novel photosensitizer, MV6401, causes selective thrombosis in tumor vessels after photodynamic therapy. *Cancer Res* 2002;62:2151-6.
5. Castano AP, Mroz P, Hamblin MR. Photodynamic therapy and anti-tumour immunity. *Nat Rev Cancer* 2006;6:535-45.
6. Kaneko K, Yamaguchi H, Saito T, et al. Hypoxia imaging endoscopy equipped with laser light source from preclinical live animal study to first-in-human subject research. *PLoS One* 2014;9:e99055.
7. Oleinick NL, Morris RL, Belichenko I. The role of apoptosis in response to photodynamic therapy: what, where, why, and how. *Photochem Photobiol Sci* 2002;1:1-21.
8. Krammer B. Vascular effects of photodynamic therapy. *Anticancer Res* 2001;21:4271-7.
9. Leroy HA, Vermandel M, Leroux B, et al. MRI assessment of treatment delivery for interstitial photodynamic therapy of high-grade glioma in a preclinical model. *Lasers Surg Med* 2018;5:460-8.
10. Haedicke K, Agemy L, Omar M, et al. High-resolution optoacoustic imaging of tissue responses to vascular-targeted therapies. *Nat Biomed Eng* 2020;4:286-97.

Department of Gastroenterology and Endoscopy, National Cancer Center Hospital East, Kashiwa, Japan.

Copyright © 2020 American Society for Gastrointestinal Endoscopy. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.vgje.2020.07.003>