

## Two Cases of Emergency Tracheostomy After Head and Neck Photoimmunotherapy

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**Abstract.** *Background/Aim: Head and neck photoimmunotherapy (HN-PIT) has been an insured treatment in Japan for approximately three years. The number of treatments has gradually increased to over 350 cases. However, there are still various questions in actual clinical practice, including laryngeal edema. Therefore, it is vital to carefully explain in advance to patients the possibility of laryngeal edema occurring and obtaining consent for tracheostomy as a prophylactic or emergency measure. At our institution, 44 HN-PIT cycles were performed in 23 patients between January 2021 and October 2023. Of these, we experienced two cases in which preventive tracheostomy was not performed because the risk of laryngeal edema was considered low; however, laryngeal edema developed after treatment, and an emergency tracheostomy had to be performed. Case Report: Case 1 was a patient in his 70s with a local recurrence of mandibular gingival carcinoma. HN-PIT using cylindrical diffusers was performed on the target lesion, extending from the lateral wall of the oropharynx to the soft palate. Case 2 was also a patient in his 70s with carcinoma of the mid-pharynx. HN-PIT was performed using a frontal diffuser to target lesions extending from the soft palate to the buccal mucosa. Notably, both patients developed laryngeal edema after*

*HN-PIT, and an emergency tracheostomy had to be performed. Conclusion: HN-PIT treatment is still being established through a trial-and-error method and is still incomplete.*

Head and neck photoimmunotherapy (HN-PIT) is a treatment designed to specifically destroy tumor cells using Cetuximab Sarotalocan Sodium, followed by irradiation with a red light at 690 nm (1-4). In Japan, HN-PIT has been approved for treating unresectable, locally advanced, and locally recurrent head and neck cancers. The number of treatments in Japan is > 350, and the numbers of clinical studies (5-8) and case reports (9-15) are gradually increasing. However, various clinical issues are encountered in actual clinical practice, including laryngeal edema. Laryngeal edema is a life-threatening adverse event; therefore, the possibility of laryngeal edema should be explained to patients, and consent should be obtained for tracheostomy as a prophylactic or emergency measure.

HN-PIT targeting lesions of the larynx, hypopharynx, and cervical lymph nodes adjacent to the larynx are more likely to cause laryngeal edema. Therefore, a prophylactic tracheostomy is strongly recommended for lesions near the larynx. However, the nasopharynx, oral cavity, oropharynx, and paranasal sinuses are located far from the larynx, and the extent of laryngeal edema due to HN-PIT remains unclear.

At our institution, we performed 44 HN-PIT cycles in 23 patients between January 2021 and October 2023. We report two cases in which laryngeal edema developed after HN-PIT and emergency tracheostomy was performed because prophylactic tracheostomy was not performed earlier as the risk of laryngeal edema was considered low.

### Case Report

Laser illumination of HN-PIT was performed using a BioBrade<sup>®</sup> laser system (Rakuten Medical Inc., San Diego, CA, USA). Laser diffusers are cylindrical diffusers with needle catheters used for large or subcutaneous tumors, and frontal diffusers are used for superficial tumors (5, 11).

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**Key Words:** Head and neck cancer, head and neck photoimmunotherapy, airway emergency, laryngeal edema, emergency tracheostomy.

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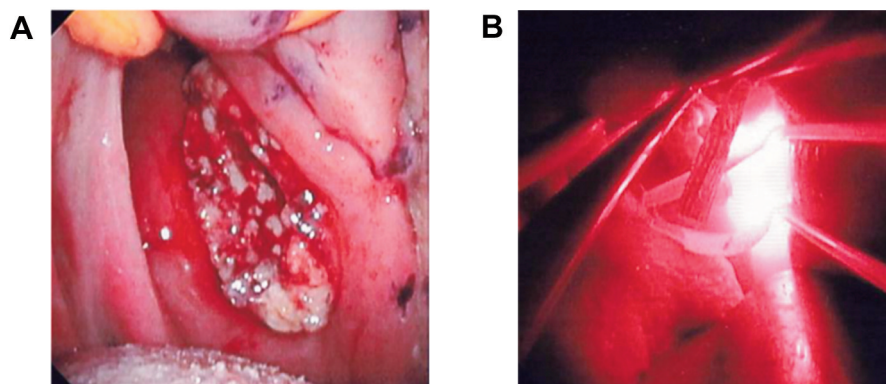


Figure 1. The lesion from the posterior to the lateral wall of the left oropharynx A) Soft palate elevated with a Nelaton catheter to define the area to be treated (yellow arrowheads). B) Laser illumination using cylindrical diffusers.

*Case 1.* The patient was a male in his 70s with a recurrence of mandibular gingival cancer in the oropharynx (rT3N0M0 Stage III squamous cell carcinoma, p16 negative). His treatment history included left mandibular segmentectomy, neck dissection, and reconstructive surgery with a scapular plus vastus latissimus dorsi musculocutaneous flap at another institution. The patient underwent postoperative radiation therapy because of the positive resection margins. He presented to our hospital with HN-PIT due to local recurrence in the lateral-to-posterior wall of the left oropharynx.

*HN-PIT Cycle 1.* The lesion was 33 mm × 22 mm in size and extended from the lateral to the posterior wall of the left oropharynx. The HN-PIT was illuminated using four cylindrical diffusers with a diameter of 20 mm each and one frontal diffuser with a spot diameter of 30 mm (Figure 1A and B).

*Steroid administration for preventing and treating edema.* During the surgery, hydrocortisone sodium succinate 500 mg was administered. Betamethasone Sodium Phosphate 8 mg was administered on the day of the operation and the first postoperative day; 4 mg was administered on the second postoperative day.

*Laryngeal edema.* Postoperative endoscopic findings of the larynx are shown in Figure 2A-D. Edema appeared in the left arytenoid region postoperatively; however, there was no airway obstruction. Therefore, no emergency tracheostomy was necessary. The edema resolved after four days.

*HN-PIT Cycle 2.* The target lesion was slightly reduced in cycle 1 but remained between the left oropharynx's lateral and the posterior wall and was 30 mm × 20 mm in size. The HN-PIT was illuminated four times using a frontal diffuser with a spot diameter of 30 mm (Figure 3A and B).

*Steroid administration for prevention and treatment of edema.* During surgery, 500 mg Methylprednisolone Sodium Succinate was administered, and 8 mg betamethasone sodium phosphate was administered postoperatively.

*Laryngeal edema.* Three hours after the end of the operation, airway constriction sounds were heard. Laryngoscopy could not confirm the site of obstruction due to swelling of the epiglottis (Figure 4A); therefore, an emergency tracheostomy was performed. The swelling of the epiglottis improved on the second postoperative day, but the edema of the arytenoid persisted until the fourth postoperative day (Figure 4B-D).

*Case 2.* The patient was a male in his 70s with a new cancer lesion in the oropharynx (upper wall) (T3N0M0 Stage III, squamous cell carcinoma, p16 negative). The patient had a history of tongue cancer (partial resection of the right tongue), tongue cancer (right tongue hemisection and free skin flap reconstruction), tongue cancer mediastinal lymph node metastasis (chemoradiotherapy), cancers of the hypopharynx and larynx (radiation therapy), and cancer of the esophagus (total resection plus gastric tube reconstruction). Endoscopic findings before HN-PIT showed a prominent lesion on the soft palate extending to the hard palate and buccal mucosa (Figure 5A). This was a newly diagnosed oropharynx cancer; however, the lesion had already been treated using radiotherapy. The patient had an Eastern Cooperative Oncology Group performance status of 1 and could not ingest orally because of dysphagia caused by stenosis of the reconstructed area after esophageal cancer surgery.

*HN-PIT Cycle 1.* Lugol's solution (0.75%) was sprayed to determine the extent of the lesion extension. The lesion was 60 mm × 50 mm, mainly an elevated tumor on the soft palate extending to the hard palate and buccal mucosa (Figure 5B).

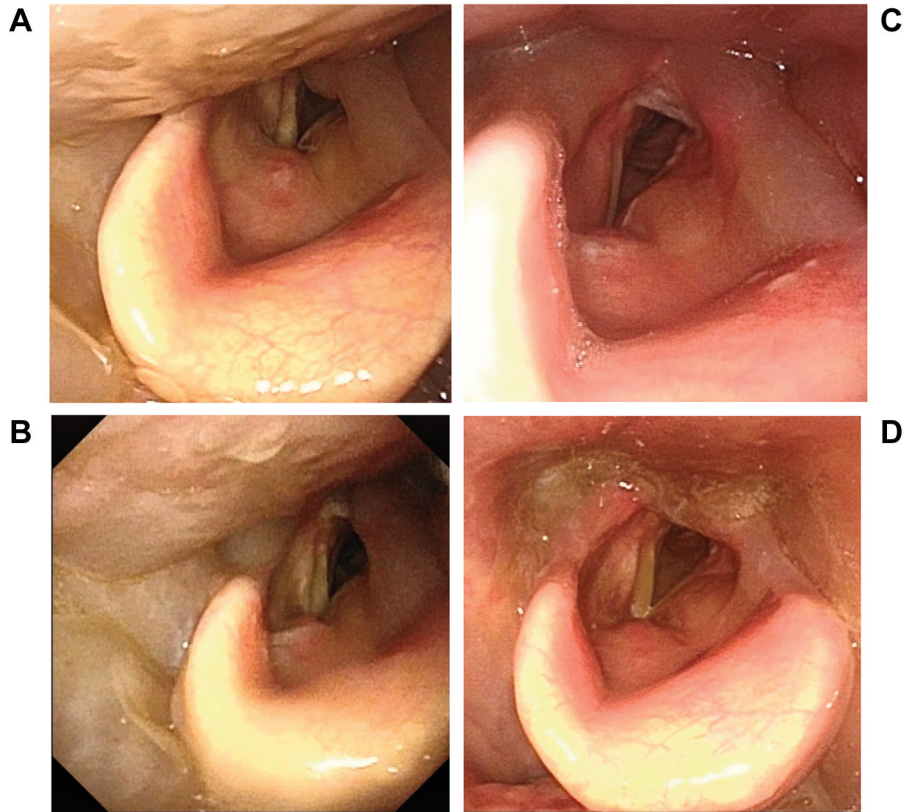


Figure 2. Endoscopic findings of the larynx after head and neck photoimmunotherapy. A) Four hours later. B) Eight hours later. C) One day later. D) Two days later.

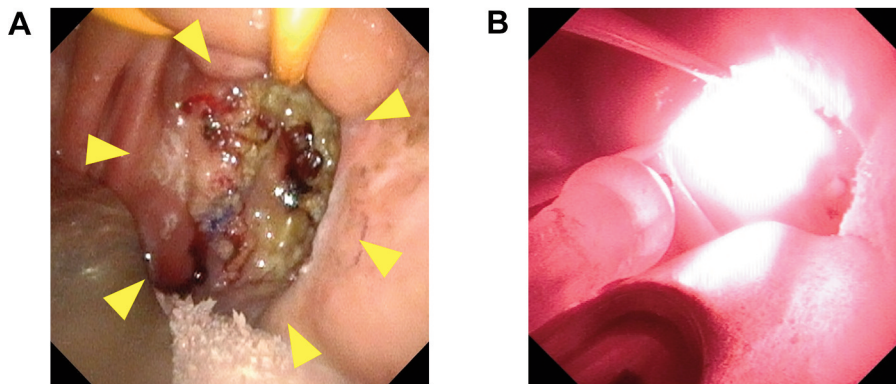


Figure 3. The lesion from the posterior to the lateral wall of the left oropharynx A) Soft palate elevated with a Neraton catheter to define the area to be treated (yellow arrowheads). B) Laser illumination using a frontal diffuser.

Therefore, HN-PIT was illuminated thrice using a frontal diffuser with a spot diameter of 38 mm (Figure 5C and D).

*Laryngeal edema.* The patient developed respiratory distress in the hospital room 6 h after surgery, with a SpO<sub>2</sub>

of 70% (O<sub>2</sub> 8 L). Edema in the right cheek, lip, and oral cavity was severe (Figure 6A), and laryngoscopy revealed significant edema in the glottis (Figure 6B). Therefore, a diagnosis of an airway obstruction emergency was made, and an emergency tracheostomy was performed. On the



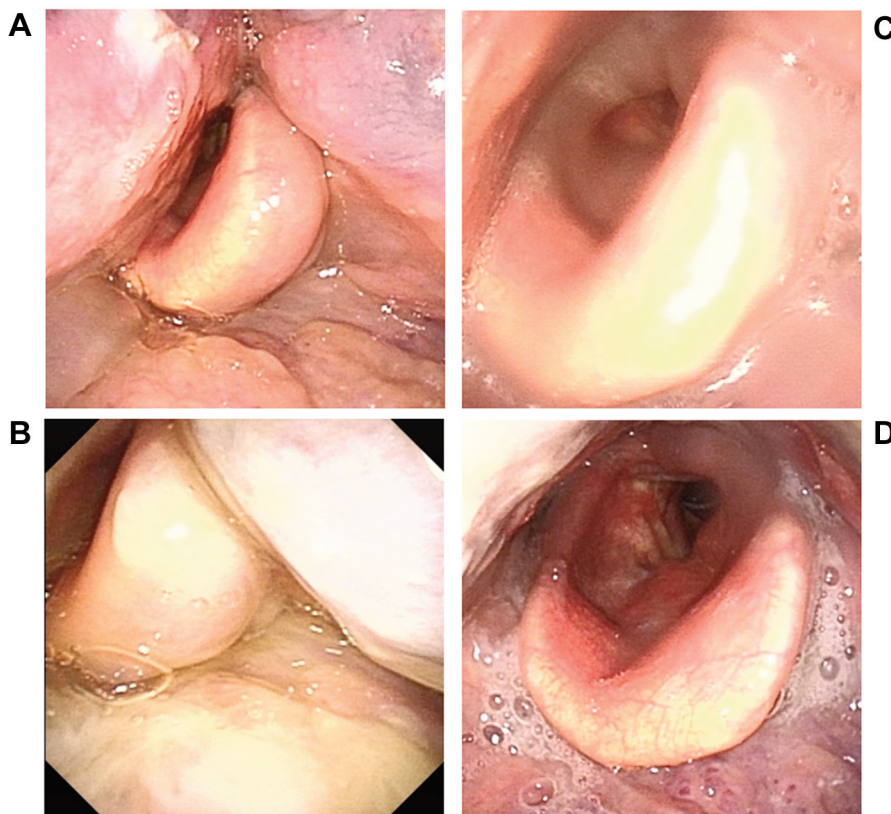


Figure 4. Endoscopic findings of laryngeal endoscopy after head and neck photoimmunotherapy. A) Three hours later. B) One day later. C) Two days later. D) Four days later.

second postoperative day, the epiglottis swelling had improved.

## Discussion

Emergency tracheostomy was performed for lesions in the oropharynx due to laryngeal edema after HN-PIT. The oropharynx is considered a low risk for laryngeal edema because of its distance from the larynx. This is a valuable case report of an airway obstruction emergency after HN-PIT. Nakajima *et al.* (16) demonstrated that near-infrared photoimmunotherapy in mice caused inflammatory edema in the tissues surrounding the illuminated tumors. However, the mechanism of edema in areas distant from the illuminated site remains unclear.

Patients undergoing HN-PIT are carefully informed of the possibility of laryngeal edema, and consent is obtained for tracheostomy as an emergency measure. Prophylactic tracheostomy is strongly recommended for HN-PIT targeting the larynx and hypopharynx because of the high likelihood of laryngeal edema. However, for HN-PIT in areas distant from the larynx, such as the oral cavity and oropharynx, there is

resistance to performing a tracheostomy in all patients considering the quality of life. Case 1 underwent HN-PIT for a target lesion in the posterior to the lateral wall of the oropharynx. Cycle 1 was illuminated mainly using a cylindrical diffuser, and a mild edema of the left laryngeal mucosa was observed. Cycle 2 was expected to cause post-illumination laryngeal edema; however, because only a frontal diffuser was used, the degree of laryngeal edema was assumed to be milder than that in cycle 1. Cycle 2 was to be performed using a cylindrical diffuser; however, mild edema was expected since only a frontal diffuser was used. In Case 2, HN-PIT was performed on a superficial target lesion in the oropharynx, from the soft palate to the buccal mucosa. The patient was illuminated at a distance from the larynx and treated only with a frontal diffuser; therefore, it was assumed that laryngeal edema would not occur significantly. The cylindrical diffuser is designed to illuminate the tissue in a cylindrical shape with a radius of 10 mm and a light dose of 100 J/cm<sup>2</sup>. The frontal diffuser is designed with a light dose of 50 J/cm<sup>2</sup> on the skin or mucous surfaces, and a distributed depth of <10 mm from the surface (5, 11). The light dose seems to be less than that of the cylindrical diffuser. However, an emergency tracheostomy

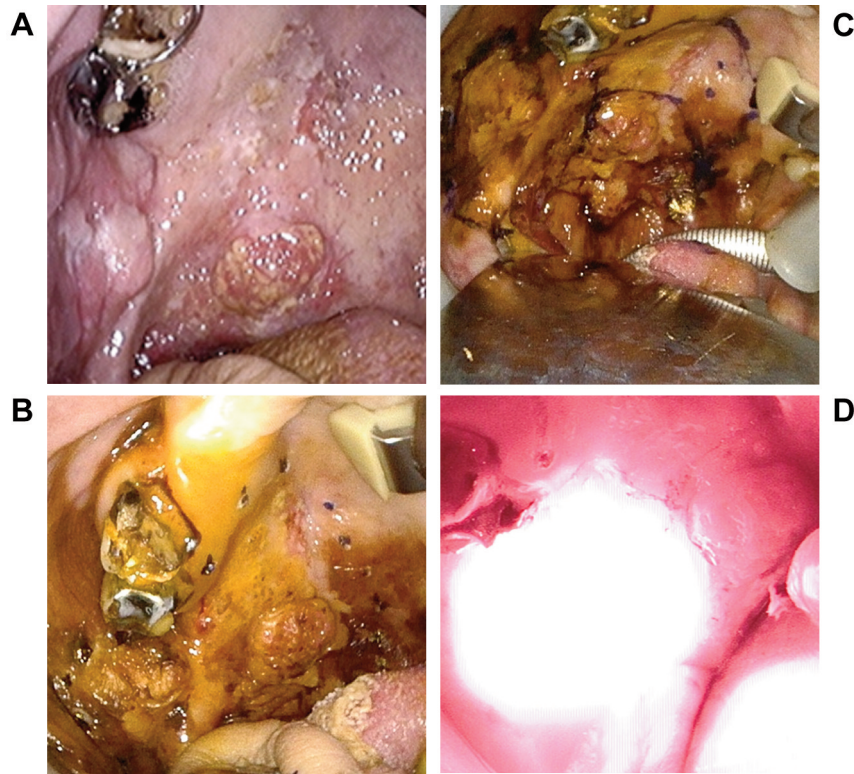


Figure 5. The lesion is an elevated tumor of the soft palate, extending to the hard palate and buccal mucosa. A) Lesion before treatment. B) Marking the lesion with Lugol's. C) Marking the area to be illuminated with a frontal diffuser. D) Laser illumination using a frontal diffuser.

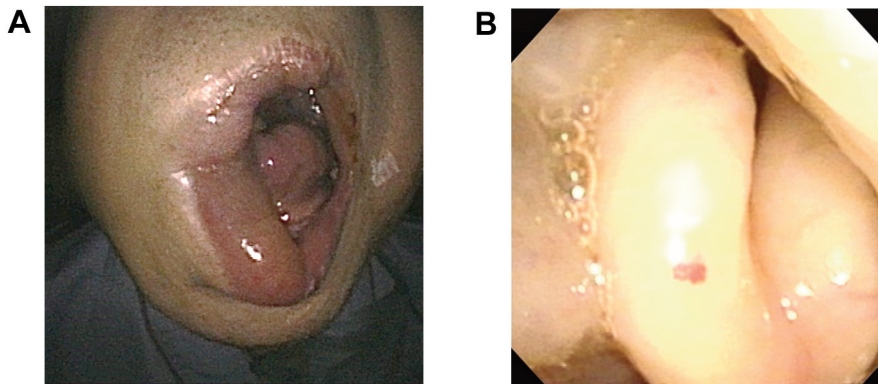


Figure 6. Findings at 6 h after head and neck photoimmunotherapy. A) Swelling of the right cheek and edema of the lip. B) Swelling of the epiglottis by endoscopy.

was performed because of unexpected laryngeal edema. In the reported case of HN-PIT requiring emergency tracheostomy, the lesion in the oropharynx was illuminated only with a frontal diffuser. The larynx was illuminated relatively extensively: four times using frontal diffusers with a spot diameter of 30 mm and thrice using frontal diffusers with a spot diameter of 38

mm. The mechanism that causes laryngeal edema by illuminating an area far from the larynx is unknown; however, the illuminated area may be a factor.

Further studies on the mechanism of laryngeal edema are required. HN-PIT may cause laryngeal edema even when illuminating areas distant from the larynx. Even when a

relatively large area is irradiated with a frontal diffuser, it is necessary to carefully explain the procedure and take measures to prevent laryngeal edema before initiating treatment.

## Conclusion

We encountered two cases of laryngeal edema after HN-PIT that required emergency tracheostomy. HN-PIT is still being established through trial and error. However, we hope that our experience provides a better view of the future of HN-PIT.

## Conflicts of Interest

Isaku Okamoto received lecturer fees from Rakuten Medical KK. The Authors declare no conflicts of interest in relation to this study.

## Authors' Contributions

Isaku Okamoto prepared the case report. Isaku Okamoto wrote the main text and prepared the figure. Isaku Okamoto, Takuro Okada, and Kunihiro Tokashiki performed the head and neck photoimmunotherapy. Isaku Okamoto, Kiyooki Tsukahara, Takuro Okada, and Kunihiro Tokashiki oversaw patient treatment. All Authors discussed the results of the case report, commented on the article, and approved the final version for publication.

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## References

- 1 Kobayashi H, Choyke PL: Near-infrared photoimmunotherapy of cancer. *Acc Chem Res* 52(8): 2332-2339, 2019. DOI: 10.1021/acs.accounts.9b00273
- 2 Mitsunaga M, Ogawa M, Kosaka N, Rosenblum LT, Choyke PL, Kobayashi H: Cancer cell-selective in vivo near infrared photoimmunotherapy targeting specific membrane molecules. *Nat Med* 17(12): 1685-1691, 2011. DOI: 10.1038/nm.2554
- 3 Ogawa M, Tomita Y, Nakamura Y, Lee MJ, Lee S, Tomita S, Nagaya T, Sato K, Yamauchi T, Iwai H, Kumar A, Haystead T, Shroff H, Choyke PL, Trepel JB, Kobayashi H: Immunogenic cancer cell death selectively induced by near infrared photoimmunotherapy initiates host tumor immunity. *Oncotarget* 8(6): 10425-10436, 2017. DOI: 10.18632/oncotarget.14425
- 4 Cognetti DM, Johnson JM, Curry JM, Kochuparambil ST, McDonald D, Mott F, Fidler MJ, Stenson K, Vasani NR, Razaq MA, Campana J, Ha P, Mann G, Ishida K, Garcia-Guzman M, Biel M, Gillenwater AM: Phase 1/2a, open-label, multicenter study of RM-1929 photoimmunotherapy in patients with locoregional, recurrent head and neck squamous cell carcinoma. *Head Neck* 43(12): 3875-3887, 2021. DOI: 10.1002/hed.26885
- 5 Tahara M, Okano S, Enokida T, Ueda Y, Fujisawa T, Shinozaki T, Tomioka T, Okano W, Biel MA, Ishida K, Hayashi R: A phase I, single-center, open-label study of RM-1929 photoimmunotherapy in Japanese patients with recurrent head and neck squamous cell carcinoma. *Int J Clin Oncol* 26(10): 1812-1821, 2021. DOI: 10.1007/s10147-021-01960-6
- 6 Okamoto I, Okada T, Tokashiki K, Tsukahara K: Quality-of-life evaluation of patients with unresectable locally advanced or locally recurrent head and neck carcinoma treated with head and neck photoimmunotherapy. *Cancers (Basel)* 14(18): 4413, 2022. DOI: 10.3390/cancers14184413
- 7 Shibutani Y, Sato H, Suzuki S, Shinozaki T, Kamata H, Sugisaki K, Kawanobe A, Uozumi S, Kawasaki T, Hayashi R: A case series on pain accompanying photoimmunotherapy for head and neck cancer. *Healthcare (Basel)* 11(6): 924, 2023. DOI: 10.3390/healthcare11060924
- 8 Shinozaki T, Matsuura K, Okano W, Tomioka T, Nishiya Y, Machida M, Hayashi R: Eligibility for photoimmunotherapy in patients with unresectable advanced or recurrent head and neck cancer and changes before and after systemic therapy. *Cancers (Basel)* 15(15): 3795, 2023. DOI: 10.3390/cancers15153795
- 9 Kushihashi Y, Masubuchi T, Okamoto I, Fushimi C, Hanyu K, Yamauchi M, Tada Y, Miura K: Photoimmunotherapy for local recurrence of nasopharyngeal carcinoma: a case report. *Int J Otolaryngol Head Neck Surg* 11(05): 258-265, 2022. DOI: 10.4236/ijohns.2022.115027
- 10 Nishikawa D, Suzuki H, Beppu S, Terada H, Sawabe M, Hanai N: Near-infrared photoimmunotherapy for oropharyngeal cancer. *Cancers (Basel)* 14(22): 5662, 2022. DOI: 10.3390/cancers14225662
- 11 Okamoto I, Okada T, Tokashiki K, Tsukahara K: A case treated with photoimmunotherapy under a navigation system for recurrent lesions of the lateral pterygoid muscle. *In Vivo* 36(2): 1035-1040, 2022. DOI: 10.21873/invivo.12799
- 12 Okamoto I, Okada T, Tokashiki K, Tsukahara K: Photoimmunotherapy for managing recurrent laryngeal cancer cervical lesions: a case report. *Case Rep Oncol* 15(1): 34-39, 2022. DOI: 10.1159/000521435
- 13 Kishikawa T, Terada H, Sawabe M, Beppu S, Nishikawa D, Suzuki H, Hanai N: Utilization of ultrasound in photoimmunotherapy for head and neck cancer: a case report. *J Ultrasound*, 2023. DOI: 10.1007/s40477-023-00774-8
- 14 Koyama S, Ehara H, Donishi R, Morisaki T, Ogura T, Taira K, Fukuhara T, Fujiwara K: Photoimmunotherapy with surgical navigation and computed tomography guidance for recurrent maxillary sinus carcinoma. *Auris Nasus Larynx* 50(4): 646-651, 2023. DOI: 10.1016/j.anl.2022.09.001
- 15 Omura G, Honma Y, Matsumoto Y, Shinozaki T, Itoyama M, Eguchi K, Sakai T, Yokoyama K, Watanabe T, Ohara A, Kato K, Yoshimoto S: Transnasal photoimmunotherapy with cetuximab sarotalocan sodium: Outcomes on the local recurrence of nasopharyngeal squamous cell carcinoma. *Auris Nasus Larynx* 50(4): 641-645, 2023. DOI: 10.1016/j.anl.2022.06.004
- 16 Nakajima K, Sugikawa A, Yasui H, Higashikawa K, Suzuki C, Natsume T, Suzuki M, Takakura H, Tomita M, Takahashi S, Hirata K, Magata Y, Kuge Y, Ogawa M: In vivo imaging of acute physiological responses after treatment of cancer with near-infrared photoimmunotherapy. *Mol Imaging Biol* 25(4): 648-658, 2023. DOI: 10.1007/s11307-023-01822-9

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