Photodiagnosis and Photodynamic Therapy 54 (2025) 104719

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Research Paper

Near-infrared photoimmunotherapy for recurrent cancer at the base of the tongue

Takuma Makino [a,*], Asami Nishikori [b], Yasuharu Sato [b], Yuto Naoi [a], Junya Matsumoto [a], Shohei Fujimoto [a], Mizuo Ando [a]

[a] Department of Otolaryngology - Head and Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
[b] Department of Hematopathology, Okayama University Graduate School of Health Sciences, Okayama, Japan

ARTICLE INFO

Keywords:
Near-infrared photoimmunotherapy (NIR-PIT)
Epidermal growth factor receptor (EGFR)
Cylindrical diffuser
Puncture interval
Base of tongue cancer

ABSTRACT

Near-infrared photoimmunotherapy (NIR-PIT) is a novel therapeutic approach that targets epidermal growth factor receptor (EGFR). In NIR-PIT, administration of cetuximab sarotalocan sodium is followed by laser irradiation of the affected area, which theoretically should induce tumor cell death. However, residual tumors are occasionally observed. This study investigated factors that influence the therapeutic efficacy of NIR-PIT in cases of recurrence of cancer at the base of the tongue. Six patients undergoing 11 treatment cycles were analyzed, focusing on the puncture interval of cylindrical diffusers and the expression of EGFR in tumors. The results demonstrated that a puncture interval of ≤12 mm significantly enhanced therapeutic efficacy, with one case achieving complete response. EGFR expression was positive in all cases and expression score showed no significant change between before and after treatment. These findings suggest that puncture interval plays a critical role in therapeutic outcomes, whereas EGFR expression may not directly influence treatment efficacy.

1. Introduction

In Japan, near-infrared photoimmunotherapy (NIR-PIT) became available for unresectable recurrent head and neck cancer in January 2021. NIR-PIT induces tumor necrosis by irradiation of the tumor with nonthermal red light (690 nm) after administration of cetuximab sarotalocan sodium, which contains IRDye700DX bound to cetuximab [1, 2].

In theory, administration of cetuximab sarotalocan sodium followed by irradiation with laser light should eradicate tumor cells; however, residual tumor cells are sometimes observed. Possible reasons for the insufficient therapeutic effect include inadequate laser irradiation and low epidermal growth factor receptor (EGFR) expression in the tumor. To the best of our knowledge, no report has thoroughly investigated these factors. In this study, we evaluated outcomes of NIR-PIT for recurrent cancer at the base of the tongue and investigated the factors influencing its therapeutic efficacy.

2. Materials and methods

2.1. Patients

The participants were six patients (11 cycles) with recurrent cancer at the base of the tongue who were treated with NIR-PIT in our department between January 2021 and December 2023. All patients had a history of prior treatments, including surgery, chemotherapy, and radiotherapy (Table 1). Based on preoperative imaging assessments, lesions situated near major arteries were excluded from eligibility for NIR-PIT, as their anatomical proximity posed a heightened risk of intraprocedural bleeding and post-treatment hemorrhage. We recorded the puncture interval during treatment with a cylindrical diffuser for each cycle, tumor size before and after treatment, and EGFR expression in collected specimens. Tumor size was measured using CT or MRI, depending on the case, and compared before and after treatment. Subtle lesions that could not be visualized by imaging were measured by direct observation. Measurements were obtained before subsequent treatment in patients who underwent additional therapy, and from clinical evaluations in patients who received no further treatment. All study protocols were approved by the institutional review board of our

* Corresponding author at: 2-5-1, Shikata-cho, Kita-ku, Okayama 700-8558, Japan.
E-mail address: makin-t@okayama-u.ac.jp (T. Makino).

https://doi.org/10.1016/j.pdpdt.2025.104719
Received 15 May 2025; Received in revised form 10 July 2025; Accepted 11 July 2025
Available online 12 July 2025

Table 1
Summary of prior treatments, including surgery, radiotherapy, and chemotherapy, in each case.

Case	Age (y)	Primary tumor site	History of surgery	History of radiotherapy and chemotherapy
①	81	Tongue	Partial tongue resection	RADPLAT, S-1
②	73	Hypopharynx	Total pharyngolaryngectomy ESD	CCRT (CDGP + 5-FU)
③	74	Hypopharynx	TOVS ESD	Radiotherapy
④	74	Hypopharynx	Total laryngectomy ESD	Radiotherapy
⑤	69	Oropharynx	Oropharyngeal resection	Pem + CDDP + 5-FU*
⑥	81	Oropharynx	Resection of tongue and floor of mouth	CCRT (CDDP + 5-FU)

RADPLAT, radiotherapy and concomitant intraarterial cisplatin; ESD, endoscopic submucosal dissection; CCRT, concomitant chemoradiotherapy; TOVS, transoral videolaryngoscopic surgery.
*Received radiotherapy for tongue cancer.

department (approval No Rin2241). Informed consent was obtained from all patients.

3. Case summaries

3.1. Case 1

Three years ago, the patient underwent concurrent chemoradiotherapy for tongue cancer, which included intra-arterial chemotherapy with cisplatin (Cisplatin, 100 mg/m^2) and radiation therapy (60 Gy). Fifteen months prior to the current presentation, local recurrence was noted in the tongue, and partial tongue resection was performed. A new recurrent lesion was detected at the base of the tongue, for which photoimmunotherapy (PIT) was subsequently administered.

3.2. Case 2

Eleven years ago, the patient received chemoradiotherapy for hypopharyngeal cancer (one cycle of Nedaplatin, 120mg/body plus 5-Fuorouracil, 750mg/body and 60 Gy of radiation). In the same year, subtotal esophagectomy was performed for concurrent esophageal cancer. Three years ago, recurrence of hypopharyngeal cancer was observed, and the patient underwent total pharyngolaryngectomy. At the present visit, a recurrent lesion at the base of the tongue was identified, and PIT was applied. Notably, the patient has undergone a total of four endoscopic submucosal dissections (ESD) for superficial pharyngeal carcinoma to date.

3.3. Case 3

The patient had received radiotherapy for base of tongue cancer (details unavailable). Four years ago, partial glossectomy was performed for tongue cancer. In the same year, cervical lymph node metastases were detected, and the patient underwent both partial glossectomy and neck dissection. Two years ago, recurrence at the base of the tongue was treated with transoral videolaryngoscopic surgery (TOVS). Upon further recurrence at the same site, PIT was administered for the recurrent lesion. Notably, the patient has undergone a total of five ESD for superficial pharyngeal and esophageal carcinoma to date.

3.4. Case 4

Twenty-three years ago, the patient underwent radiotherapy (70 Gy) for glottic cancer. One year later, recurrence was noted, and the patient underwent total laryngectomy and neck dissection. Five years ago, recurrence in the oropharynx was identified, and oropharyngeal tumor resection with neck dissection was performed. Two years ago, the patient underwent ESD for superficial oropharyngeal carcinoma and subtotal esophagectomy for concurrent esophageal cancer. A new recurrence at the base of the tongue was observed, and PIT was applied to the lesion.

3.5. Case 5

Eighteen years ago, the patient received partial resection of tongue and oropharyngeal, and chemoradiotherapy for tongue cancer (details unavailable). One year later, metastatic pulmonary lesions were detected and treated with partial lung resection. Three years ago, recurrence at the base of the tongue and metastatic pulmonary lesions were identified, and chemotherapy with pembrolizumab, cisplatin, and 5-Fuorouracil was initiated. Due to tumor progression, the regimen was switched to cetuximab and paclitaxel. While both lesions showed partial response, they remained persistent. Further chemotherapy was deemed infeasible due to the development of paclitaxel-induced retinopathy. Therefore, partial lung resection was performed for the pulmonary metastases, and PIT was applied to the tumor at the base of the tongue,

3.6. Case 6

Six years ago, the patient underwent resection of partial tongue and floor of mouth, and neck dissection for tongue cancer, followed by postoperative chemoradiotherapy (two cycles of Cisplatin, 100mg/body plus 5-Fuorouracil, 800mg/body, and 60 Gy of radiation). Six months ago, recurrence was observed extending from the lateral wall of the oropharynx to the base of the tongue, for which partial pharyngectomy was performed. A subsequent recurrence at the base of the tongue was identified, and PIT was administered for this lesion.

4. Immunohistochemistry and EGFR evaluation

Paraffin-embedded tissue sections were used for IHC staining with the EGFR antibody (1:200, ab52894, Abcam) using an automated BOND Max stainer (Leica Biosystems, Wetzlar, Germany). EGFR scoring was conducted using the method described by Robert et al., with evaluations performed by a single pathologist [3]. For sections with analyzable tumor cells, membrane staining intensity was classified into four categories: no staining (0), weak staining (1+, light brown membrane staining visible only under high magnification), intermediate staining (2+, between 1+ and 3+), and strong staining (3+, dark brown linear membrane staining visible under low magnification). Using prospectively collected immunohistochemistry data, an EGFR immunohistochemistry score was generated on a continuous scale ranging from 0 to 300. The score was calculated by integrating staining intensity and frequency data, using the following formula:

$$1 \times (\text{percentage of cells staining weakly}[1+]) \\ +2 \times (\text{percentage of cells staining moderately}[2+]) \\ +3 \times (\text{percentage of cells staining strongly}[3+]).$$

5. Results

Mean patient age was 75.3 years, all of whom were male. The primary tumor sites included the hypopharynx (3 cases), oropharynx (2 cases), and tongue (1 case). All tumors were histopathologically diagnosed as squamous cell carcinoma. In all cycles, a cylindrical diffuser was used, and no cycles involved the use of a frontal diffuser. Frontal diffusers require perpendicular irradiation to the target lesion. However, due to anatomical constraints, perpendicular irradiation is not feasible for recurrent lesions at the base of the tongue. Therefore, laser light was delivered via puncture from the neck using a cylindrical diffuser. Puncture sites for cylindrical diffusers were generally confirmed using ultrasound and fiberoptic endoscopy guidance. Despite a history of

various prior treatments in all cases, scarring was minimal and did not interfere with the puncture procedures. In patients who had not undergone total laryngectomy, tracheostomy was performed to prevent airway obstruction.

Tumor enlargement was observed in two cycles where cylindrical diffusers were inserted at 18 mm intervals. Among the five cycles with 15 mm intervals, both tumor reduction and enlargement were noted. All cases with punctures at 12 or 10 mm intervals showed a reduction in size (Table 2). In Case 4, the tumor reduced to the point where it could no longer be measured, and complete response was achieved in Case 5. Tumor evaluation was not conducted for the third cycle of Case 1 or the first cycle of Case 6.

Mild pain (CTCAE Grade 1–2) was observed in all cases, and localized edema occurred in several patients, which resolved within a few days without intervention. No severe adverse events such as bleeding, fistula formation, or infection were observed during the study. Additionally, despite prior surgical and radiotherapeutic interventions, no technical difficulties related to puncture or increased risk of complications were encountered. Preventive tracheostomy was performed in patients without prior laryngectomy to avoid airway obstruction. Overall, the morbidity associated with NIR-PIT in this cohort was considered low.

EGFR immunostaining was performed on specimens obtained before and after NIR-PIT. EGFR positivity was observed in all evaluable cases. There was no difference in EGFR score between before and after treatment in any patient (Table 3 and Fig. 1).

6. Discussion

In this study, we hypothesized two possible causes of variability in the treatment efficacy of NIR-PIT: (1) insufficient laser light irradiation to the tumor, and (2) low EGFR expression in the tumor, and found that shorter puncture intervals provided better treatment results whereas EGFR expression status was not relevant.

Although puncture intervals of 16–18 mm were originally recommended, many clinicians in real-world practice perceived that these intervals resulted in suboptimal efficacy. Accordingly, in our institution, puncture intervals were progressively shortened with increasing treatment experience [4]. To minimize bias, we limited our analysis to cases for which NIR-PIT was performed by a single operator in the same tumor subregion, focusing exclusively on the two factors mentioned above. Regarding puncture interval, all cycles with 12 mm and 10 mm intervals showed tumor reduction, with some achieving complete response. However, given the heterogeneity of tumor tissues, the extent of light penetration within the tumor may not be fully determined by puncture interval alone. We will continue to accumulate cases to enable statistical analysis and further evaluate this treatment. In addition, as light attenuation can vary depending on the tumor type, more detailed basic medical studies are needed to examine the actual extent of laser light irradiation within the tumor.

EGFR immunostaining was positive in all cases, with no significant difference in EGFR score between the pre- and post-treatment specimens. If NIR-PIT effectively eliminated tumor cells expressing EGFR, a reduction in EGFR-expressing cells and lower scores would be expected post-treatment. However, no significant changes were observed, suggesting that EGFR-expressing cells may persist after treatment. One possible explanation is that cetuximab sarotalocan sodium may not bind to all EGFR-expressing cells, which warrants further investigation.

This study has several limitations. As this is a novel treatment, the sample size was inherently small. Furthermore, limiting the analysis to a single tumor subregion further reduced the number of cases, making statistical analysis infeasible. However, this approach was necessary to eliminate confounding factors such as differences in tumor subregions, treatment methods, or operators. Additionally, the timing of evaluations differed. Ideally, tumor size and pathological evaluations would be conducted at consistent intervals post-treatment. However, given the retrospective nature of the study using clinical specimens, this was challenging. Although we were unable to quantify the precise increase in laser light delivery resulting from shortening the puncture interval from 18 mm to 10 mm, treatment efficacy appeared to improve, and no apparent increase in complications was observed. Nonetheless, it is important to note that the present study was not designed to comprehensively assess the safety of shorter puncture intervals. Therefore, although the observed outcomes are promising, further accumulation of clinical cases and careful evaluation of safety are warranted before broad clinical application. Despite these limitations, we believe our analysis provides valuable insights into the treatment efficacy of NIR-PIT.

7. Conclusion

Puncturing and irradiating with cylindrical diffusers at 12 mm or 10 mm intervals appeared to enhance the treatment efficacy of NIR-PIT. Of note, EGFR expression was observed in all cases, with no significant difference in expression scores before and after treatment. These findings suggest that EGFR expression may have limited relevance to the treatment efficacy of NIR-PIT.

Table 2
Insertion intervals of cylindrical diffusers and corresponding changes in tumor size before and after NIR-PIT.

Case	Cycle	Number of diffusers used	Puncture interval (mm)	Tumor size before NIR-PIT (mm)	Tumor size after NIR-PIT (mm)
①	1st	CD20 × 4	18	10 × 20 × 20	18 × 20 × 20 (POD27)
	2nd	CD20 × 4	18	18 × 20 × 20	15 × 26 × 20 (POD25)
	3rd	CD20 × 2 + CD30 × 3	15	15 × 26 × 20	NA
②	1st	CD20 × 4 + CD30 × 1	15	25 × 20 × 27	15 × 20 × 20 (POD48)
	2nd	CD20 × 3	15	15 × 20 × 20	23 × 21 × 23 (POD27)
③	1st	CD20 × 4 + CD30 × 1	15	24 × 17 × 25	20 × 15 × 20 (POD41)
	2nd	CD20 × 5	15	20 × 15 × 20	19 × 16 × 22 (POD22)
④	1st	CD20 × 8	12	32 × 0 × 15	28 × 0 × 10 (POD43)
	2nd	CD20 × 7	10	28 × 0 × 10	Almost CR (POD63)
⑤	1st	CD20 × 10	10	20 × 9 × 19	CR (POD68)
⑥	1st	CD20 × 5	10	18 × 10 × 18	NA

CD, cylindrical diffuser; CR, complete response; NIR-PIT, near-infrared photoimmunotherapy; NA, not available; POD, postoperative day.
The term "0 mm" indicates that the tumor is a superficial carcinoma that cannot be visualized on imaging.

Table 3
EGFR expression scores in each case and changes before and after NIR-PIT, where available.

Case	Cycle	EGFR score before NIR-PIT	EGFR score after NIR-PIT
①	1st	272	-
②	1st	290	278 (POD28)
	2nd	278	291 (POD32)
③	2nd	270	197 (POD27)
④	1st	234	228 (POD49)
	2nd	228	209 (POD72)
⑤	1st	287	-
⑥	1st	226	-

EGFR, epidermal growth factor receptor; NIR-PIT, near-infrared photoimmunotherapy; POD, postoperative day.
"–" indicates no available specimen for evaluation.

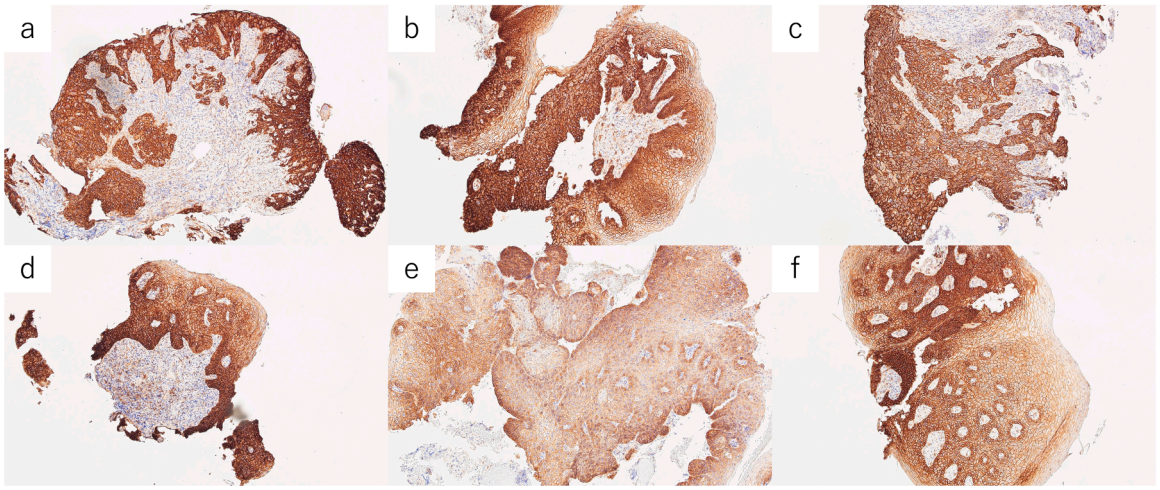

Fig. 1. EGFR immunostaining. (a) Pre-treatment, (b) post-cycle 1, and (c) post-cycle 2 specimens of case 2. (d) Pre-treatment (e) post-cycle 1, and (f) post-cycle 2 specimens of case 4.

CRediT authorship contribution statement

Takuma Makino: Writing – original draft, Visualization, Validation, Investigation, Funding acquisition, Data curation, Conceptualization. **Asami Nishikori:** Writing – review & editing, Investigation. **Yasuharu Sato:** Writing – review & editing, Resources, Investigation. **Yuto Naoi:** Writing – review & editing, Validation, Investigation. **Junya Matsumoto:** Writing – review & editing, Validation, Investigation. **Shohei Fujimoto:** Writing – review & editing, Validation, Investigation. **Mizuo Ando:** Writing – review & editing, Supervision.

Disclosure statement

All authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by a JSPS KAKENHI Grant-in-Aid for Early-Career Scientists No JP23K15888.

References

[1] D.M. Cognetti, J.M. Johnson, J.M. Curry, S.T. Kochuparambil, D. McDonald, F. Mott, et al., 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 (2021) 3875–3887.

[2] M. Tahara, S. Okano, T. Enokida, Y. Ueda, T. Fujisawa, T. Shinozaki, et al., 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 (2021) 1812–1821.

[3] P. Robert, R.P. Jose, v P Joachim, K. Maciej, R. Rodryg, P. Keunchil, et al., EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study, Lancet Oncol. 13 (2012) 33–42.

[4] T. Makino, Y. Sato, K. Uraguchi, Y. Naoi, Y. Fukuda, M. Ando, Near-infrared photoimmunotherapy for salivary duct carcinoma, Auris Nasus Larynx 51 (2) (2024) 323–327.