

Predictive Factors for the Efficacy of Head and Neck Photoimmunotherapy and Optimization of Treatment Schedules

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Abstract

Background/Aim: Head and neck photoimmunotherapy (HN-PIT) is a promising treatment for unresectable locally advanced or recurrent head and neck cancers. However, the optimal tumor characteristics and treatment schedules remain unclear. This study aimed to identify factors associated with treatment efficacy and assess the effectiveness of treatment schedules. **Patients and Methods:** A retrospective cohort study of patients treated with HN-PIT at Aichi Cancer Center Hospital from January 2021 to October 2024 was conducted. Tumor characteristics, treatment cycles, and outcomes were analyzed. The thickness and longest diameter of the tumors were evaluated, and treatment intervals were assessed for their association with complete response (CR).

Results: Among the 19 patients (30 cycles), CR was observed exclusively in local lesions. Smaller and thinner lesions showed significantly better treatment responses. Thinner lesions were more likely to achieve CR after a single cycle, whereas intermediate-thickness tumors often required multiple cycles with shorter intervals. The regional lesions did not achieve CR, even with multiple cycles and shorter intervals. Age was a significant factor influencing CR.

Conclusion: HN-PIT demonstrated promising efficacy for local lesions, particularly for smaller and thinner lesions. Optimizing treatment schedules, including shorter intervals for intermediate lesions, is critical for improving outcomes. Further research is needed to enhance the efficacy for regional lesions and refine treatment schedules.

Keywords: Photoimmunotherapy, head and neck cancer, tumor thickness, treatment intervals, laser illumination.

Introduction

Head and neck cancer is the seventh most common type of cancer worldwide (1). Surgical treatment for recurrent head

and neck cancer in patients who have previously undergone radiation or surgery has a high risk of serious complications (2-4). Consequently, chemotherapy, molecular-targeted agents, or immune checkpoint inhibitors are commonly



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selected treatments (5-7). However, these treatments have low cure rates, even for localized disease (8). Therefore, curative treatments for lesions that are unsuitable for radiation and surgery are needed.

Head and neck photoimmunotherapy (HN-PIT) is an emerging treatment developed to achieve local control of head and neck cancers by combining laser illumination with administration of an antibody-photosensitizer conjugate (9). Cetuximab sarotalocan sodium, an antibody-photosensitizer conjugate, consists of cetuximab, an epidermal growth factor receptor monoclonal antibody, and IR700, a photosensitizing dye. After administering cetuximab sarotalocan sodium, illumination with 690-nm laser light selectively destroys the tumor cells. In a phase I/IIa, multicenter, open-label trial of HN-PIT, the overall response rate was 43.3% [95% confidence interval (CI)=25.46-62.57%], median overall survival was 9.30 months (95%CI=5.16-16.92), and median progression-free survival was 5.16 months (95%CI=2.10-5.52) (10).

Since January 2021, HN-PIT has been an available treatment option in Japan for unresectable locally advanced or locally recurrent head and neck cancer in patients ineligible for radiation due to a history of previous radiotherapy or other factors. Over the past four years, real-world clinical experience has provided significant insights leading to an improved understanding of its clinical effects and applications (11-14). Despite these advancements, knowledge regarding the most appropriate targeted tumors and treatment schedules for HN-PIT remains limited, which hinders optimization of its clinical use. The responsiveness to HN-PIT can vary even for same-sized tumors. Most tumors completely disappear after the same number of treatment cycles, but not all. Although the instructions for use specify that intervals between cycles should be ≥ 28 days up to four cycles, the optimal number of cycles and appropriate interval remain unclear.

The study aim was to determine the characteristics of tumors with high treatment efficacy and identify the most effective treatment schedules for HN-PIT.

Patients and Methods

Treatment. Cetuximab sarotalocan sodium was administered intravenously at a dose of 640 mg/m². At 20 to 28 h post-administration, laser illumination with the BioBlade® laser system (Rakuten Medical, Inc., Tokyo, Japan) was performed in the operating room on patients under general anesthesia. There are two types of laser illumination methods: frontal diffusers and cylindrical diffusers (Figure 1). The frontal diffuser is used to illuminate from the surface, and the cylindrical diffuser delivers light from a needle catheter inserted into the deeper tissues. Depending on the tumor's location and size, these methods can be used individually or in combination. If the treatment effect is insufficient, additional treatments can be administered up to a maximum of four cycles, with an interval of ≥ 28 days between treatments.

Study design. This retrospective cohort study included patients treated with HN-PIT at the Aichi Cancer Center Hospital from January 2021 to October 2024. The study was approved by the institutional review board [IRB approval number: (2024-0-409)]. The inclusion criteria were patients diagnosed with unresectable locally advanced or locally recurrent head and neck squamous cell carcinoma. Patients with carotid artery invasive lesions or radiation therapy-suitable lesions were excluded.

Data collection. The patient demographic data, clinical characteristics, and treatment information were retrospectively extracted from the medical records. The collected data included age, sex, tumor location, tumor size, treatment cycle, and outcomes, such as treatment response. Data were anonymized before analysis to ensure patient confidentiality. Computed tomography (CT) and magnetic resonance imaging (MRI) images were acquired to measure each tumor's longest diameter and thickness assessed during pretreatment. The longest diameter of the tumor was defined as the maximum linear measurement of the lesion. The tumor thickness was defined as the maximum perpendicular distance from the skin or

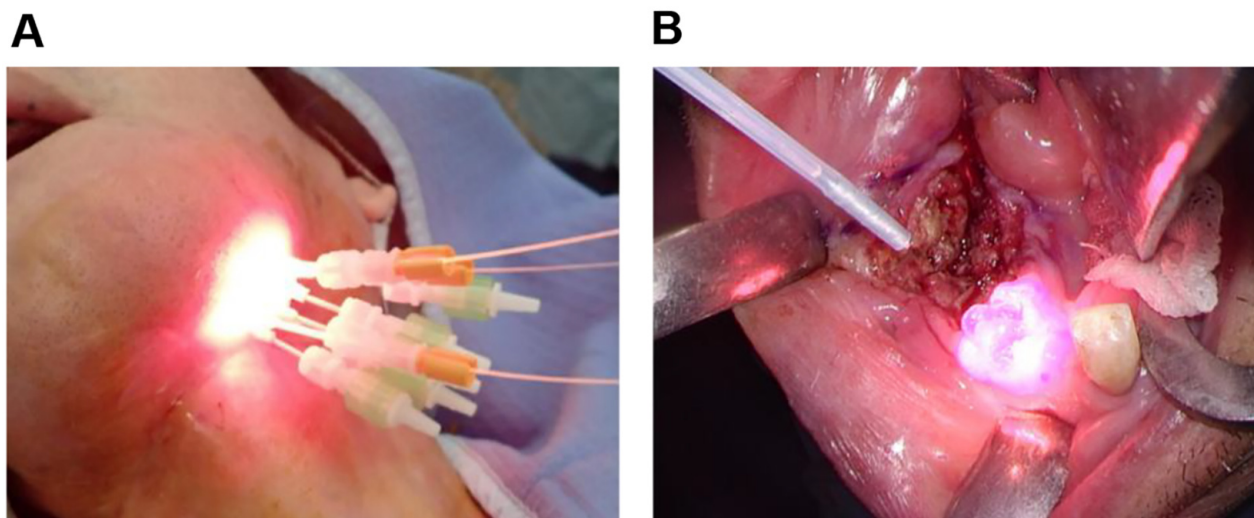


Figure 1. Illumination with two types of diffusers: (A) Cylindrical diffuser for a cervical lesion. (B) Frontal diffuser for a gingival lesion.

mucosal surface to the deepest portion of the tumor measured at the thickest section.

Response criteria. The treatment response was assessed according to the modified RECIST (mRECIST) criteria (15), which is specifically designed to assess the efficacy of locoregional therapies by focusing on the viable tumor, defined as the portion showing enhancement on contrast-enhanced imaging. Non-enhancing areas, such as necrotic or fibrotic regions, were excluded from the evaluation. In HN-PIT, rapid tumor collapse often leads to formation of necrotic tissue, which can cause overestimation of the tumor's size by conventional RECIST. Therefore, this study used mRECIST.

The tumor response was classified into the following categories according to the mRECIST criteria below. Complete response (CR): the disappearance of any intratumoral arterial enhancement in all target lesions; partial response (PR): $\geq 30\%$ decrease in the sum of the diameters of viable (contrast enhancement in the arterial phase) target lesions; stable disease: any cases that do not qualify for either PR or progressive disease (PD). PD: an increase of $\geq 20\%$ in the sum of the diameters of viable (enhancing) target lesions.

Evaluation schedule. Contrast-enhanced imaging modalities, including computed tomography (CT) or magnetic resonance imaging (MRI), performed at baseline and at regular intervals (*e.g.*, every 1-3 months), were used to assess the treatment responses.

Statistical analysis. EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) was used to perform all statistical analyses. The relationship between each variable and CR was analyzed. The treatment aim was to achieve local control, thus it was important to identify the characteristics that increase the likelihood of achieving CR. Lesions that do not achieve CR typically progress and become challenging to manage. Fisher's exact test and t-test were used to identify factors associated with CR. Values of $p < 0.05$ were accepted as indicating statistical significance.

Ethics statement. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Patient data were anonymized, and no patient-identifying information was used.

Table I. Patient characteristics.

Features	n=19
Age (years), median (IQR)	75 (42-88)
Sex	
Male	17 (89%)
Female	2 (11%)
ECOG-PS	
0	7 (37%)
1	11 (58%)
2	1 (5%)
Illumination site	
Local	15 (79%)
Regional	4 (21%)
Primary site	
Oral cavity	10 (53%)
Oropharynx p16 (-)	5 (26%)
Maxillary sinus	1 (5%)
Larynx	1 (5%)
Nasopharynx	1 (5%)
Hypopharynx	1 (5%)
Nasal cavity	1 (5%)
Tumor size (mm)	
Longest diameter (mm)	20 (7-75)
Thickness (mm)	9 (1-54)
Cycle	
1	9 (47%)
2	4 (21%)
3	4 (21%)
4-	2 (11%)
Prophylactic tracheostomy	
Yes	6 (32%)
No	11 (58%)
Permanent tracheostomy	2 (11%)
Prior treatment	
Radiation	19 (%)
Surgery	17 (%)
Chemotherapy	1 (5%)
Immune checkpoint inhibitor	1 (5%)

IQR: Interquartile range; ECOG PS: Eastern Cooperative Oncology Group performance status.

Results

Patient characteristics. A total of 19 patients met the inclusion criteria, and 30 cycles of HN-PIT were performed. The patient characteristics are shown in Table I. The median age was 75 years (range=42-88 years), and there were 17 males and two females. The most common primary site was the oral cavity (10 cases), followed by the oropharynx (five cases).

Table II. Illuminated site.

Site	N=19
Local lesion (N=15)	
Oral cavity	7
Oropharynx p16(-)	3
Oropharynx + Hypopharynx	1
Nasopharynx	1
Larynx	1
Maxillary sinus	1
Nasal cavity	1
Reginal lesion (N=4)	
Cervical lymph node	4

Illumination for local lesions was performed in 15 cases, and illumination for regional lesions was performed in four cases. The specific distribution of the illuminated sites was as follows: oral cavity (n=7), oropharynx (n=3), sinonasal region (n=2), larynx (n=1), nasopharynx (n=1), and oropharynx plus hypopharynx (n=1) for local illumination (Table II). For regional illumination, all lesions were located on the cervical sites (n=4). Of these, three cases involved skin infiltration. The median longest diameter of the lesions was 20 mm (range=7-75 mm), and the median thickness was 9 mm (range=1-54 mm). The treatment cycle distribution was as follows: one cycle in nine patients, two cycles in four patients, three cycles in four patients, and four or more cycles in two patients. Prophylactic tracheostomy was performed in eight patients.

Factors associated with treatment outcomes. The treatment response was analyzed separately for local and regional lesions (Table III). Only local lesions showed CRs (Figure 2); therefore, factors associated with CR were investigated only in patients with local lesions. Among the 14 cases of local lesions, seven achieved CR; of these, five remained recurrence-free during follow-up, whereas two developed cervical recurrence and were subsequently treated with chemotherapy. For regional lesions, one case developed a new lesion shortly after illumination, whereas two cases showed PR before the emergence of

Table III. Factors associated with complete response in local lesions.

	CR	PR	PD	<i>p</i> -Value
Age				0.015
≤75	7	1	0	
>75	1	4	2	
Sex				0.62
Male	6	5	2	
Female	2	0	0	
Illumination site				0.93
Oral cavity	4	2	2	
Pharynx	2	2	0	
Others	2	1	0	
Cycle				1.00
1	4	3	2	
2	2	1	0	
3	2	1	0	
Longest diameter				0.013
Short (<20 mm)	5	1	0	
Intermediate (20-50 mm)	3	4	0	
Long (>50 mm)	0	0	2	
Thickness				0.031
Thin (<10 mm)	6	3	0	
Intermediate (10-30 mm)	2	2	0	
Thick (>30 mm)	0	0	2	

CR: Complete response; PR: partial response; PD: progressive disease.

new lesions, so alternative treatments were performed subsequently. The analysis indicated that age was significantly associated with achieving CR ($p=0.01$), suggesting that younger patients (≤ 75 years) were more likely to achieve CR. No significant associations were found between achieving CR and patient sex, illumination site, or the number of treatment cycles.

The relationship between tumor size and CR was also examined. The tumor size was evaluated on the basis of both the longest diameter and thickness. Tumors were classified into three categories on the basis of their longest diameter as short (<20 mm), intermediate (20-50 mm), and long (>50 mm), and on the basis of their thickness as thin (<10 mm), intermediate (10-30 mm), and thick (>30 mm). Both the longest diameter and thickness were significantly associated with treatment response, with a higher incidence of CR observed in the smaller and thinner categories ($p=0.013$ and $p=0.031$, respectively).

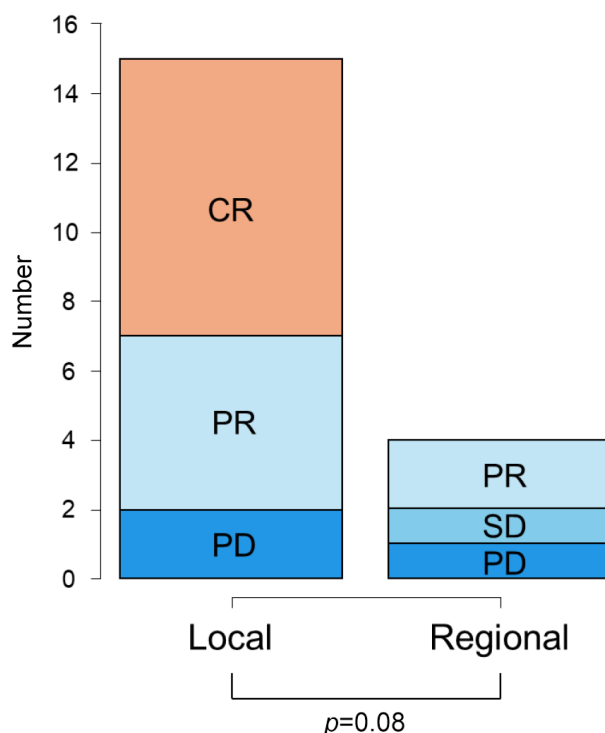


Figure 2. Treatment response of local and regional lesions after head and neck photoimmunotherapy. CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Treatment cycles and intervals. The relationships between the treatment cycles, tumor thickness, and efficacy were further investigated (Figure 3). Specifically, most thin lesions achieved CR after a single treatment cycle. Among the thin lesions that failed to achieve CR, the following scenarios were noted: one patient declined a second treatment cycle, one patient exhibited necrosis rendering the assessment of tumor persistence inconclusive, and one patient had a vocal-cord lesion for which three treatment cycles were performed, but a residual tumor remained. All intermediate lesions achieving CR required two or more treatment cycles. For multiple-cycle treatments in local lesions, achieving CR was more common when at least one treatment interval was ≤ 50 days. Two cases with longer treatment intervals failed to achieve CR, even for thin tumors (2 and 8 mm). Despite the short treatment intervals, no cases of regional lesions

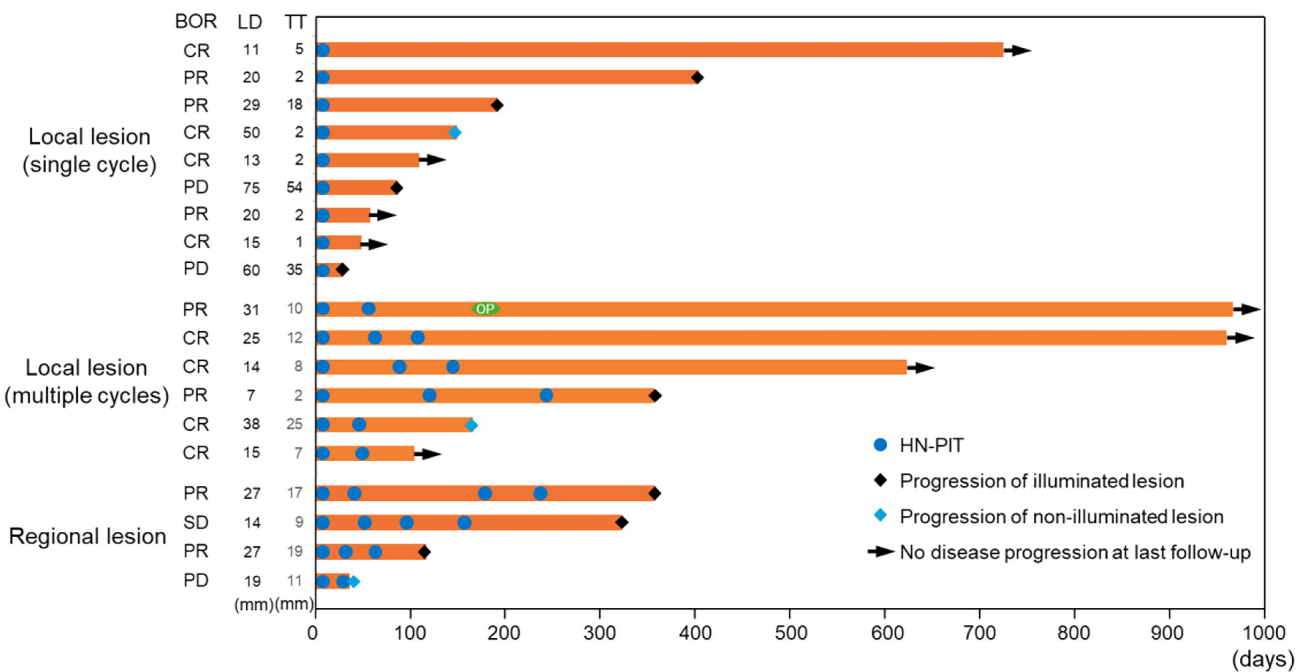


Figure 3. Association between tumor size and complete response (CR) in local lesions: A) Longest tumor diameter: median of 22 mm for CR, median of 34 mm for non-CR. B) Tumor thickness: median of 7 mm for CR, median of 17 mm for non-CR.

achieved CR. A comparison of the shortest treatment intervals for local lesion cases treated with multiple cycles revealed that the interval was significantly shorter in the cases that achieved CR ($p=0.039$) (Figure 4). Conversely, thick lesions progressed rapidly to PD after a single cycle, necessitating a switch to alternative therapies, such as immune checkpoint inhibitors or cytotoxic drugs.

Discussion

This study sought to identify the characteristics of tumors that are most likely to achieve a CR after HN-PIT and to determine the most effective treatment schedules for this emerging modality. To the best of our knowledge, this is the first study to explore the relationship between HN-PIT and tumor location, size, patient age, and treatment intervals.

A key observation in this study was the observed fundamental difference in the treatment responses

between local and regional lesions. The CRs were observed exclusively in the local lesions, whereas the regional lesions failed to achieve a CR despite similar treatment approaches. This response difference suggests that tumor characteristics and the microenvironment of regional lesions may decrease their responsiveness to HN-PIT (16, 17). It is notable that recurrent regional lesions after surgery or radiotherapy are often associated with extracapsular extension, and skin metastasis may also be present. In this study, three out of four regional lesions exhibited skin infiltration, with one lesion presenting as a skin metastasis. In preclinical mouse models, the combination of PIT with immune checkpoint inhibitors reportedly enhanced therapeutic efficacy, suggesting that combination therapy with HN-PIT and immune checkpoint inhibitors may be necessary to improve outcomes in regional settings in the future (18-22). In clinical practice, Hirakawa *et al.* reported favorable treatment responses when combining HN-PIT with

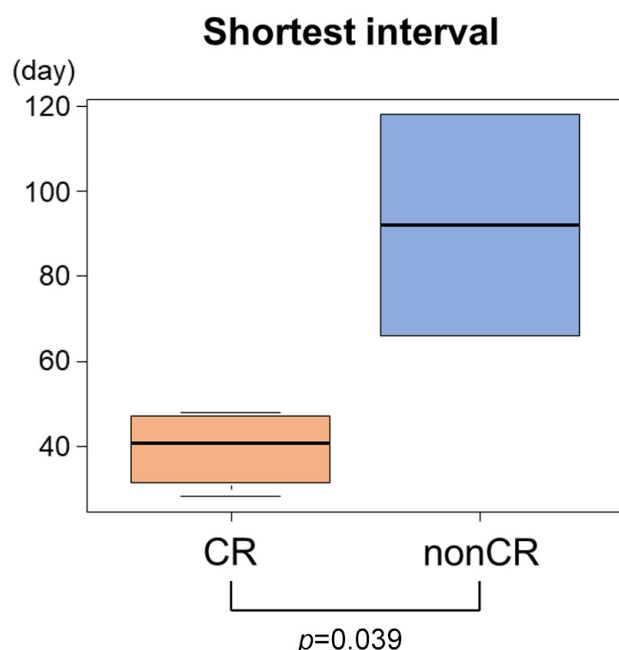


Figure 4. Swimmer's plot from the time of head and neck photo-immunotherapy to disease progression. In local lesions, thinner tumors were more likely to achieve complete response (CR) after a single treatment cycle. Lesions with intermediate thickness often required multiple treatment cycles, frequently with shorter cycle intervals. In the regional lesions, CR was not observed, even with multiple treatment cycles and shorter intervals.

immune checkpoint inhibitors for the treatment of head and neck squamous cell carcinoma (23).

Younger patients (≤ 75 years) were more likely than older patients to achieve CR. This difference may be attributed to several age-related factors, such as immune function, overall physiological resilience, and tissue-repair capacity. A meta-analysis of chemotherapy for head and neck cancer showed that the effectiveness of chemotherapy decreased with age (24, 25), whereas other studies on chemotherapy, immune checkpoint inhibitors, and photodynamic therapy have reported minimal differences in treatment efficacy between elderly and younger patients (26-29). We previously reported a significant increase in damage-associated molecular patterns, such as high-mobility group box 1, after HN-PIT in patients with head and neck cancer (30). Immune function also has been documented to

decline with age, which may explain the better therapeutic response observed in younger patients after HN-PIT (31).

The trend observed regarding tumor size was another significant aspect of this study. Smaller tumor size was significantly associated with a higher likelihood of achieving CR. Similarly, in photodynamic therapy, there are reports supporting the greater effectiveness of treatment for smaller tumors (17, 32-34). This observation aligns with the concept that localized treatments, such as HN-PIT, are more effective when the tumor burden is smaller given that larger tumors may present challenges related to adequate light penetration and homogeneous drug distribution. Previous studies on NIR-PIT have demonstrated uneven drug distribution within tumors, with accumulation often concentrated on the tumor surface (35, 36). In addition, achieving sufficient coverage of the entire tumor by laser illumination requires combining surface illumination with interstitial illumination using diffusers for larger or deeper tumors (37). Even with these approaches, complete coverage of larger tumors might be challenging, potentially resulting in suboptimal therapeutic effects. Therefore, early intervention when tumors are smaller may enhance treatment outcomes, and this observation should be considered in future treatment planning.

Treatment intervals also emerged as a critical factor in achieving CR. For thin tumors, a single treatment cycle may suffice for the reasons mentioned earlier. However, for intermediately thick tumors, multiple treatment cycles may be required to achieve CR, with shorter intervals between treatments associated with higher CR rates. This suggests that reducing the interval between treatment cycles could help maintain an effective therapeutic influence on the tumor and prevent regrowth during the waiting period. Conversely, for thin tumors that fail to achieve CR, consecutive treatments with intentionally short intervals may be necessary. For tumors with intermediate or greater thickness, scheduling of subsequent treatment cycles in advance to ensure timely reillumination is important. To achieve this, effective

management of adverse events and ensuring patient understanding are crucial.

Study limitations. First, the small sample size limits the generalizability of the findings for HN-PIT, a relatively new treatment, thus warranting studies with larger samples. Second, the retrospective nature of the study may have introduced biases in treatment selection and scheduling. Prospective comparative trials with larger cohorts are needed to validate the findings presented here and to establish more definitive conclusions regarding the efficacy of HN-PIT.

Conclusion

To improve the efficacy of HN-PIT for head and neck cancer, it is essential to base treatment schedules on tumor thickness. Further research is needed to improve the outcomes for regional lesions and establish optimal treatment schedules. By optimizing this therapy, HN-PIT potentially can become an important treatment option for head and neck cancer.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization: D.N., T.S.; Acquisition of data: D.N., T.S., H.S., S.B., H.T., Y.K., N.H.; Formal analysis and interpretation of the data, methodology: D.N., T.S.; writing – original draft preparation, D.N.; Revising the manuscript for intellectual content – review and editing: D.N., T.S., H.S., S.B., H.T., Y.K., N.H.; All Authors have read and agreed to the published version of the manuscript.

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