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Original Research

Clinical feasibility of induction chemotherapy with paclitaxel, carboplatin, and cetuximab (PCE therapy) prior to definitive therapy in patients with oral squamous cell carcinoma: A preliminary retrospective study

Kotaro Sakurai [a,*], Hideharu Abe [b], Shuichi Imaue [a], Atsushi Ikeda [a], Akira Nakazato [b], Michiro Fujisaka [b], Tomohiko Kutsuna [c], Ryuji Hayashi [d], Yuka Morita [b], Shin-ichi Yamada [a]

[a] Department of Oral and Maxillofacial Surgery, Faculty of Medicine, Academic Assembly, University of Toyama, Toyama city, Toyama, Japan
[b] Department of Otorhinolaryngology, Head and Neck Surgery, Faculty of Medicine, Academic Assembly, University of Toyama, Toyama city, Toyama, Japan
[c] Department of Oral and Maxillofacial Surgery, Toyama City Hospital, Toyama city, Toyama, Japan
[d] Department of Clinical Oncology, Faculty of Medicine, Academic Assembly, University of Toyama, Toyama city, Toyama, Japan

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ABSTRACT

Objective: Evidence regarding paclitaxel, carboplatin, and cetuximab (PCE) administered as induction chemotherapy (ICT) prior to definitive therapy in patients with oral squamous cell carcinoma (OSCC) remains limited. This study aimed to describe the feasibility and tolerability of PCE administered prior to definitive therapy in patients with OSCC.

Methods: Forty-three patients who underwent PCE prior to definitive therapy for OSCC were included. Data was retrospectively analyzed using medical records. Radiologic response was assessed according to RECIST criteria and overall response rate (ORR), disease control rate (DCR). Safety and relationships between radiologic response and histological treatment effect were descriptively summarized.

Results: The radiologic response showed an ORR of 83%, a DCR of 95%. In the 32 patients underwent surgical treatment, downstaging was observed in 25 of 32 (78%) patients for the T factor, and 19 of 24 (79%) patients for the N factor. Recurrence was observed in four patients. In adverse events, grade 3/4 neutropenia and febrile neutropenia occurred in 21 (49%) and 3 (7%) patients, respectively. No delay in the initiation of definitive therapy because of adverse events was noted.

Conclusions: PCE administered as ICT prior to definitive therapy was associated with a high rate of radiologic response and frequent tumor downstaging among patients who subsequently underwent surgery. Although substantial hematologic toxicity, including frequent grade 3/4 neutropenia, was observed, treatment-related delays to definitive therapy were not observed, suggesting that this approach is feasible in patients with OSCC when appropriate toxicity management is applied.

1. Introduction

Surgery is the standard first-line of treatment for oral squamous cell carcinoma (OSCC). In head and neck oncology, induction chemotherapy (ICT) has been explored as an initial systemic approach before definitive local therapy, primarily to reduce tumor burden and to inform subsequent treatment strategies such as organ preservation or assessment of resectability. However, the clinical role of ICT is diverse and has been reported as initial systemic therapy prior to definitive therapy, including as a bridging strategy during unavoidable delays to surgery or radiation therapy, or to achieve temporary disease control [1].

Currently, little is known about the evidence for induction

Abbreviations: OSCC, Oral squamous cell carcinoma; PCE, Paclitaxel, carboplatin, and cetuximab; ICT, Induction chemotherapy; PF, Cisplatin and fluorouracil; TPF, Docetaxel, cisplatin, and fluorouracil; ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; CTCAE, Common Terminology Criteria for Adverse Events; RECIST, Response Evaluation Criteria in Solid Tumors; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive; ORR, Overall response rate; DCR, Disease control rate; OS, Overall survival; FN, Febrile neutropenia; NCCN, National Comprehensive Cancer Network.

* Correspondence to: Department of Oral and Maxillofacial Surgery, Faculty of Medicine, University of Toyama, 2630 Sugitani, Toyama city, Toyama 930-0194, Japan.

E-mail address: sakurai@med.u-toyama.ac.jp (K. Sakurai).

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chemotherapy in OSCC, unlike in laryngopharyngeal or esophageal cancers, where functional preservation (such as laryngeal preservation) has been established [2].

Previously, conventional cytotoxic anticancer drug combination regimens, including cisplatin and fluorouracil/docetaxel, cisplatin, and fluorouracil (ICT-PF/TPF), have been reported [3–8]. However, according to the latest Japanese oral cancer treatment guidelines, systematic reviews indicate that ICT-PF/TPF shows low efficacy, low certainty of evidence, and is highly harmful [9].

Recently, the effectiveness of paclitaxel, carboplatin, and cetuximab (PCE) therapy, in which the molecular-targeted anti-epidermal growth factor receptor antibody cetuximab is added to paclitaxel and carboplatin, has been reported [10]. PCE therapy has shown clinical activity in unresectable recurrent/metastatic head and neck cancer [11–13]. However, data regarding PCE as ICT (ICT-PCE) prior to definitive therapy in OSCC remain scarce and are limited to small case series, leaving its clinical feasibility and tolerability insufficiently characterized [12].

Therefore, this study aimed to describe the feasibility and tolerability of ICT-PCE administered prior to definitive therapy in patients with OSCC. In this study, ICT was defined as initial systemic chemotherapy administered prior to definitive therapy (surgery or radiotherapy), with the intent of disease control during the pre-treatment interval and potential tumor burden reduction, rather than to guide treatment selection or organ preservation.

2. Material and Methods

2.1. Patient selection

Inclusion criteria included a diagnosis of OSCC at the departments of otolaryngology–head and neck surgery and oral and maxillofacial surgery at our hospital between January 2018 and August 2024 and treatment with ICT-PCE prior to definitive therapy. A total of 43 patients met these criteria and were included in the study. The exclusion criteria were as follows: (1) lack of histological confirmation; (2) secondary disease; (3) receipt of any prior treatment; and (4) patients judged to be unsuitable for inclusion by the principal investigator. Patient selection is summarized in a STROBE-compliant flow diagram (Fig 1).

PCE was administered in selected patients when a delay before definitive therapy was anticipated due to clinical or logistical reasons, and when temporary disease control was considered necessary based on tumor behavior.

Regarding patients who underwent surgery, in accordance with the guidelines, the safety margin is 10 mm from the primary lesion [9]. No reduction of the extent of resection was performed.

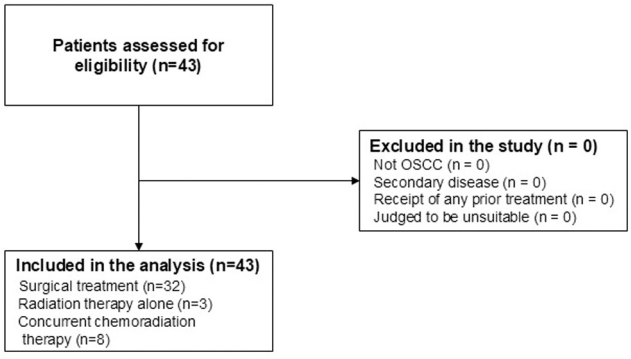

Fig. 1. STROBE flow diagram of patient inclusion. This flowchart illustrates the process of patient identification, inclusion, and exclusion in this retrospective study of PCE administered prior to definitive therapy in patients with oral squamous cell carcinoma.

2.2. Ethical considerations

This study was approved by Research Ethics Committee for Clinical and Epidemiological Research of Toyama University (approval No.: R2024080, approval date: 29 July 2024). Due to the retrospective observational nature of this study, informed consent was obtained using an opt-in/opt-out approach. The PCE regimen itself was reviewed and approved through institutional ethical deliberation, and written informed consent was obtained from all patients prior to its administration. The non-standard nature of the regimen was explained to patients verbally.

2.3. Data collection

Data was retrospectively reviewed through medical records. Observation data included gender, age at initial consultation, primary tumor site, Eastern Cooperative Oncology Group (ECOG) performance status (PS), differentiation, TNM classification 8th edition [14], treatment effect, number of PCE therapy cycles, adverse events, surgical margin status, histological treatment effect [15], prognosis, and observation period. Adverse events were evaluated based on Common Terminology Criteria for Adverse Events (CTCAE) ver.5.0 [16]. Radiologic response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [17], with responses categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), and summarized using the overall response rate (ORR) and disease control rate (DCR).

In this study, tumor responses according to RECIST criteria were evaluated by experienced oral and maxillofacial surgeons who were directly involved in the clinical management of the patients. Adverse events were evaluated on a per-patient basis, and the highest-grade toxicity observed during the entire treatment period was recorded for each patient. Relationships between radiologic response and histological treatment effect were assessed. Downstaging was defined as a decrease in either the clinical T or N category after PCE compared with baseline staging.

2.4. Dosage and administration of PCE

The PCE therapy protocol consisted of paclitaxel (100 mg/m^2) and carboplatin AUC 2.5 on days 1 and 8, with cetuximab initially at 400 mg/m^2 on day 1, followed by 250 mg/m^2 on days 8 and 15. This was considered one cycle, and 1–3 cycles were administered before definitive therapy [10]. Regarding patients aged 75 or older or those experiencing Grade 2 adverse events, paclitaxel and carboplatin doses were reduced by 20% stepwise. When adverse events of Grade 3 or higher occurred, cetuximab alone was considered.

2.5. Statistical analysis

This study was descriptive in nature. No formal hypothesis testing or inferential statistical analyses were performed. Categorical variables are summarized as frequencies and percentages, and continuous variables are summarized using medians and ranges, as appropriate. An exploratory analysis was also performed to evaluate the association between treatment exposure and treatment response according to dose modification and the number of administered cycles.

3. Results

3.1. Patient characteristics

Patients' characteristics were summarized in Table 1. Of the 43 patients, 30 (70%) were male and 13 (30%) were female, with ages ranging from 50 to 90 years (median, 73 years). The ECOG PS distribution was 0, 1, and 2 in 18 (42%), 24 (56%), and 1 (2%) patient, respectively. The

Table 1
Patient characteristics (n = 43).

Characteristic	No. of patients (%)
Age years (median [range])	73(50−90)
Gender	
Male	30(70%)
Female	13(30%)
Performance status	
0	18(42%)
1	24(56%)
2	1(2%)
Site of primary tumor	
Tongue	17(40%)
Lower gingiva	11(26%)
Upper gingiva	9(21%)
Lip	2(5%)
Buccal mucosa	2(5%)
Intraosseous carcinoma of the jaw	2(5%)
Stage	
II	3(7%)
III	4(9%)
IVa	28(65%)
IVb	8(19%)
Cycle of PCE	
1	22(51%)
2	15(35%)
3	6(14%)
Differentiation	
Well	18(42%)
Moderate	20(47%)
Poor	5(11%)
Response to PCE	
CR	1(2%)
PR	35(81%)
SD	5(12%)
PD	2(5%)
Definitive therapy	
Surgical treatment	32(74%)
Radiation therapy alone	3(7%)
Concurrent chemoradiation therapy	8(16%)

Abbreviation: PCE, paclitaxel, carboplatin, and cetuximab; CR, complete response; PR, partial response; SD, stable disease; PD progressive disease

observation period ranged from 12 to 83 months (median, 21 months). The primary sites included tongue in 17 (40%) patients, lower gingiva in 11 (26%) patients, upper gingiva in 9 (21%) patients, lip in 2 (5%) patients, buccal mucosa in 2 (5%) patients, and intraosseous carcinoma of the jaw in 2 (5%) patients. The distribution was determined to be Stage II in 3 (7%) patients, Stage III in 4 (9%) patients, Stage IVA in 28 (65%) patients, and Stage IVB in 8 (19%) patients. Treatment cycles included one course in 22 (51%) patients, two courses in 15 (35%) patients, and three courses in 6 (14%) patients. Histological analysis showed good differentiation in 18 (42%) patients, moderate differentiation in 20 (47%) patients, and poor differentiation in 5 (11%) patients. Definitive therapy consisted of surgical treatment in 32 (74%) patients, radiation therapy alone in 3 (7%) patients, and chemoradiation therapy in 8 (16%) patients.

3.2. Response to PCE

The best response to PCE was CR in 1 (2%) patient, PR in 35 (81%) patients, SD in 5 (12%) patients, and PD in 2 (5%) patients, resulting in an ORR of 83% and a DCR of 95% (Table 1).

An exploratory analysis was performed to evaluate the potential association between treatment modification and response. The ORR was 82% in 38 patients who underwent dose reduction and 100% in 5 patients who did not. According to treatment exposure, the ORR was 86% in 22 patients receiving one cycle and 76% in 21 patients receiving two or more cycles.

Among the 32 patients who underwent surgical treatment, the relationship between the response to PCE and the histological treatment effect showed that one CR patient achieved Grade 3 (3%). Of the 26 PR patients, 1 (3%) patient achieved Grade 3, 7 (22%) patients achieved Grade 2, 5 (16%) patients achieved Grade 1b, and 13 (41%) patients achieved Grade 1a. Three SD patients were Grade 1b, and two PD patients were Grade 1a (Table 2). Moreover, among these surgical patients, downstaging was observed in 25 of 32 (78%) patients for the T factor, and 19 of 24 (79%) patients for the N factor (Tables 3 and 4). The histological treatment effect was Grade 1a in 15 (47%) patients, Grade 1b in 8 (25%) patients, Grade 2 in 7 (22%) patients, and Grade 3 in 2 (6%) patients (Table 5).

Regarding the relationship between the histological treatment effect and margin status, three (20%) patients with Grade 1a and three (37%) patients with Grade 1b showed closed margins, and all patients with Grade 2/3 showed negative margins (Table 5). Recurrence occurred in four (9%) patients; one showed vertical margin closure, and the histological treatment effect was Grade 1a and Garde 1b in two patients each (Table 6). During a median follow-up of 21 months, 10 deaths were observed. OS was recorded to characterize follow-up.

3.3. Toxicity by PCE

Grade 2 or lower adverse events occurred in all 43 patients (173 incidents), whereas Grade 3 or higher adverse events occurred in 25 patients (49 incidents, 58%). Grade 3/4 neutropenia occurred in 21 (49%) patients, and febrile neutropenia (FN) occurred in 3 (7%) patients (Table 7). No delay in the initiation of definitive therapy because of adverse events was noted.

An exploratory analysis was performed to evaluate the potential association between treatment modification and severe adverse events. Grade 3 or higher adverse events occurred in 3 of 5 patients who did not undergo dose reduction (5 incidents, 60%), whereas they occurred in 22 of 38 patients who underwent dose reduction (44 incidents, 58%). According to treatment exposure, grade 3 or higher adverse events occurred in 15 of 22 patients (29 incidents, 68%) receiving one cycle and in 10 of 21 patients (20 incidents, 48%) receiving two or more cycles.

4. Discussion

This study aimed to describe the feasibility of administering ICT-PCE prior to definitive therapy in patients with OSCC. In this cohort, the treatment resulted in radiologic responses and disease control in most patients. Although grade 3/4 hematologic toxicities were common, treatment-related delays to definitive therapy were not observed. These observations support the feasibility of administering ICT-PCE prior to definitive therapy in patients with OSCC.

Current evidence supporting ICT for OSCC remains limited. Japanese oral cancer treatment guidelines weakly recommend against the use of ICT-PF/TPF [9], and major international guidelines likewise do not

Table 2
Relation between radiologic response to PCE and histological treatment effect (n = 32). Radiologic and histopathologic responses were assessed independently; any observed relationship is exploratory.

Radiologic response to PCE	No. of patients (%)	Histological treatment effect (Grade)	No. of patients (%)
CR	1(3%)	3	1(3%)
PR	26(81%)	3	1(3%)
		2	7(22%)
		1b	5(16%)
		1a	13(41%)
SD	3(9%)	1b	3(9%)
PD	2(6%)	1a	2(6%)
Total	32(100%)		32(100%)

Abbreviation: PCE, paclitaxel, carboplatin, and cetuximab; CR, complete response; PR, partial response; SD, stable disease; PD progressive disease

Table 3
Downstaging of T factor after PCE. (n = 32).

	No evidence of malignancy	ypT1	ypT2	ypT3	ypT4a
cT2	2	4	1		
cT3		3	5	2	1
cT4a	2	1	1	3	3
cT4b		1	1		2

Table 4
Downstaging of N factor after PCE. (n = 24).

	No evidence of malignancy	ypN1	ypN3a	ypN3b
cN0				
cN1	4	2		
cN2b	4	4		2
cN2c	6	1	1	

Table 5
Relation between histological treatment effect and status of margin (n = 32).

Histological treatment effect (Grade)	No. of patients (%)	Horizontal margin		Vertical margin	
		clear	closed	clear	closed
1a	15(47%)	15		12	3
1b	8(25%)	6	2	5	3
2	7(22%)	7		7	
3	2(6%)	2		2	
Total	32(100%)	30	2	26	6

Table 6
Relation between status of margin, response to treatment and histological treatment effect in recurrence cases (n = 4).

Site of recurrence	Horizontal margin	Vertical margin	Response to treatment	Histological treatment effect (grade)
Neck, Local	Clear	Clear	PD	1a
Neck	Clear	Clear	SD	1a
Local	Clear	Clear	PR	1b
Local	Clear	Closed	PR	1b

Abbreviation: PR, partial response; SD, stable disease; PD progressive disease

Table 7
Adverse events.

Type of adverse events	All grade	Grade1, 2	Grade3, 4
	n (%)	n (%)	n (%)
Hematologic toxicity			
Leukopenia	34(79%)	14(33%)	20(47%)
Neutropenia	34(79%)	13(31%)	21(49%)
Anemia	19(44%)	17(40%)	2(5%)
Thrombocytopenia	2(5%)	1(2%)	1(2%)
Nonhematologic toxicity			
Acne-like rash	25(58%)	24(56%)	1(2%)
High AST	22(51%)	22(51%)	0
Fatigue	16(37%)	16(37%)	0
High ALT	15(35%)	15(35%)	0
Constipation	11(26%)	11(26%)	0
Loss of appetite	11(26%)	11(26%)	0
Hair removal	10(23%)	10(23%)	0
Oral mucositis	5(11%)	5(11%)	0
Paronychia	5(11%)	5(11%)	0
Diarrhea	4(9%)	4(9%)	0
Nausea	4(9%)	4(9%)	0
Febrile neutropenia	3(7%)	0	3(7%)
High Creatinine	1(2%)	1(2%)	0
Hyponatremia	1(2%)	0	1(2%)

endorse ICT as standard therapy in this setting. In the 2025 revised National Comprehensive Cancer Network (NCCN) guidelines, PCE-based regimens are mentioned only as a possible option in highly selected cases of advanced, is not recommended for routine use in OSCC [2]. Accordingly, ICT-PCE, should be regarded as non-standard and investigational in this population.

Six reports on ICT-PF/TPF for oral cancer have not demonstrated consistent survival benefits [4,5,7,18–20]. However, some reports indicate that patients with a high histological response to ICT-PF/TPF show better local control and prevention of distant metastases than poor responders or non-ICT-PF/TPF patients [5,19].

TPF therapy showed Grade 3/4 neutropenia in 77–83% and FN in 5–12% of patients in the TAX and GORTEC trials, with treatment-related deaths occurring in up to 6.6% of cases [21–23]. Such toxicity profiles may make subsequent chemoradiotherapy completion difficult. Accordingly, the NCCN guidelines do not recommend cisplatin-combined chemoradiation therapy after TPF therapy [2].

PCE therapy was first reported in 2010 as a new treatment of advanced head and neck cancer [10]. A review of the literature identified four reports describing the use of ICT-PCE for head and neck cancer showed an ORR of 55.6–96%, with Grade 3/4 neutropenia in 11.4–58% and FN in 0–4.3% of patients (Table 8) [10,12,24,25]. Notably, in these reports, patients with OSCC represented only a small proportion of the study populations, accounting for approximately 2–4.5% of cases (Table 8). Accordingly, evidence specifically addressing the use of PCE prior to definitive therapy in OSCC remains limited.

The ORR observed in our study (83%) was higher than that reported by Takeshita et al. (55.6%) [25]. Several differences between the two cohorts may partly explain this discrepancy. Compared with the study by Takeshita et al., our cohort included older patients, a higher proportion of stage IV disease, and a greater proportion of patients receiving multiple cycles of PCE chemotherapy, reflecting differences in both patient characteristics and treatment exposure. However, because both studies were retrospective and treatment strategies differed between institutions, direct comparisons should be interpreted with caution. Additionally, dose reductions were frequently implemented in our

Table 8
Summary of published reports of PCE administered prior to definitive therapy in head and neck cancer. Outcomes across studies should be interpreted with caution due to differences in patient populations, disease sites, treatment settings, and study designs. The data are presented for contextual reference only and are not intended to support direct comparisons or conclusions regarding relative efficacy.

Authors	Disease site, No.	Reported outcomes	Neutropenia (Grade3/4)	Febrile neutropenia
Kies, et al.[10] (2010)	Locally advanced head and neck cancer, 47 cases (including oropharyngeal cancer 41cases, oral cancer 1 case)	ORR : 96%	21%	0%
Enokida, et al.[12] (2020)	Inoperable laryngopharyngeal cancer, 35 cases	ORR : 88.6% 3 years OS : 83.5%	11.4%	0%
Shirasu, et al.[24] (2020)	Inoperable head and neck cancer, 22 cases (including oral cancer 1 case)	ORR : 83%	58%	4%
Takeshita, et al.[25] (2025)	Operable oral cancer, 23cases	ORR : 55.6%	13%	4.3%
Our study	Oral cancer, 43 cases	ORR : 83%	49%	7%

Abbreviation: PCE, paclitaxel, carboplatin, and cetuximab; ORR, overall response rate; OS, overall survival

cohort because treatment modification was predefined for elderly patients or those experiencing adverse events. Exploratory analyses did not demonstrate a clear dose–response relationship between dose modification or treatment exposure and ORR. The apparent differences in response according to treatment exposure may be influenced by the small sample size and potential differences in patient characteristics between groups. These findings suggest that dose modification for safety may not necessarily compromise treatment efficacy in this relatively elderly population.

Adverse events occurred in all patients in this study. Of particular note, hematological toxicity occurred in approximately 80% of patients, and skin and liver disorders occurred in approximately half of patients. Grade 3/4 neutropenia occurring in 49% and FN in 7% were observed. Importantly, treatment-related delays to definitive therapy were not observed. When severe adverse events occurred, dose reduction or switching to cetuximab monotherapy was considered. These findings suggest that careful management of adverse events is important to avoid delays in definitive therapy. In exploratory analyses, the higher incidence of grade 3 or higher adverse events in patients receiving only one cycle may reflect selection bias, as patients who experienced early toxicity may have discontinued treatment after the first cycle. Consequently, patients who tolerated treatment better were more likely to receive additional cycles. However, these findings should be interpreted cautiously given the limited sample size.

With regard to ICT, delaying the initiation of definitive therapy is important. Enokida et al. reported that 34 of 35 (97%) patients completed the PCE [12]. While 2 (6%) patients could not start definitive therapy due to worsening PS from disease progression and post-PEG complications, 32 of 35 (91%) patients completed PCE and began definitive therapy [12]. In this study, all the patients began definitive therapy without delay, suggesting high completion rates with PCE.

Currently no scientific basis for a reduction surgery is shown in oral cancer. Comparing clinical staging with the histological treatment effect, PCE showed approximately 80% downstaging of both T and N factors, suggesting a potential reduction in postsurgical recurrence. Additionally, in cases where downstaging is observed, there is a possibility that conversion therapy can be applied to inoperable cases. Although the relationship between surgical specimen margins and recurrence was investigated, the sample size was too small, requiring further investigation.

In this retrospective cohort, radiologic responses according to RECIST were observed in a substantial proportion of patients. Given the limited sample size, retrospective design, and relatively short follow-up duration, these findings should be interpreted as descriptive rather than indicative of treatment efficacy. Moreover, radiologic response and histopathologic treatment effect represent distinct assessment modalities, and although an exploratory relationship was observed, no validated or predictive correlation between them can be assumed. Furthermore, discrepancies were identified between radiologic and histologic assessments, such as cases demonstrating PR according to RECIST criteria but only Grade 1a histological treatment effect. These findings underscore the complexity of response evaluation and suggest that radiologic response alone may not fully capture the biological impact of chemotherapy, highlighting the need for cautious interpretation and further investigation. Tsujikawa et al. suggested that treatment effects may vary based on cancer and immune cell composition in tissues, emphasizing the importance of exploring ICT indications based on tissue information [26].

This study has several limitations. First, it was a retrospective observational analysis conducted at a single institution, with a relatively small sample size and a short follow-up period. Therefore, the findings should be interpreted as preliminary and descriptive in nature. Future multicenter studies with larger cohorts and longer follow-up are warranted to better characterize clinical outcomes. Second, given the noncomparative study design and the heterogeneity of subsequent definitive therapy, response metrics in this study should not be interpreted as indicators of treatment efficacy. In addition, response evaluation was performed by treating oral and maxillofacial surgeons without independent radiologic validation or formal assessment of interobserver agreement, which may have introduced assessment bias.

A strength of this study is that it describes clinical experience with ICT-PCE administered prior to definitive therapy in a cohort limited to patients with OSCC. Further case accumulation and multicenter data collection are warranted to better characterize its clinical feasibility and patient selection.

5. Conclusion

ICT-PCE administered prior to definitive therapy resulted in frequent radiologic responses and tumor downstaging, and despite substantial hematologic toxicities, did not delay definitive treatment, supporting its feasibility in OSCC when appropriate toxicity management is applied. Further case studies and data collection are required.

Ethical approval

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Toyama University Hospital (R2024080). Due to the retrospective observational nature of this study, informed consent was obtained using an opt-in/opt-out approach. This study was conducted according to the guidelines of the Declaration of Helsinki.

Declaration of Competing Interest

All authors declare that they have no conflict of interest.

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