Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology

journal homepage: www.journals.elsevier.com/journal-of-oral-and-maxillofacial-surgery-medicine-and-pathology

Association between immune-related adverse events and treatment efficacy in patients with oral squamous cell carcinoma receiving immune checkpoint inhibitors

Kotaro Sakurai [a,*], Shuichi Imaue [a], Atsushi Ikeda [a], Akinari Sakurai [b], Hidetake Tachinami [a], Danki Takatsuka [a], Mitsuna Fujiki [b], Shin-ichi Yamada [a]

[a] Department of Oral and Maxillofacial Surgery, Faculty of Medicine, Academic Assembly, University of Toyama, Japan
[b] Department of Oral and Maxillofacial Surgery, Saiseikai Toyama Hospital, Japan

ARTICLE INFO

Keywords:
Immune checkpoint inhibitors
Immune-related adverse events
Oral squamous cell carcinoma
Treatment efficacy
Survival analysis

ABSTRACT

Objective: This retrospective study examined the relationship between the efficacy of immune checkpoint inhibitors (ICIs) and immune-related adverse events (irAEs) in patients with recurrent or metastatic oral squamous cell carcinoma (OSCC).

Methods: Forty patients who received ICIs as their initial treatment were included in the analysis, which utilized medical records. The severity of irAEs was evaluated according to the Common Terminology Criteria for Adverse Events version 5.0. Treatment outcomes were evaluated based on the overall response rate (ORR), disease control rate (DCR), overall survival (OS), and progression-free survival (PFS).

Results: Twenty-two irAEs were observed in 15 patients, after a median follow-up period of 15.5 months. Treatment response was significantly higher in irAE+ patients for ORR (66.7 %) and DCR (93.3 %) compared to irAE- patients (28.0 %, 48.0 %). The median OS was 36 months for irAE+ patients and 12 months for irAE- patients ($P < 0.01$). Similarly, the median PFS was 10 months for irAE+ patients and 2 months for irAE- patients ($P < 0.05$). Multivariate analysis identified irAE occurrence (hazard ratio [HR]: 0.3; 95 % confidence interval [CI]: 0.07–0.9; $P < 0.05$) as independent factors for prolonged OS.

Conclusions: These results revealed a significant correlation between irAE occurrence and improved clinical outcomes. IrAEs could potentially serve as biomarkers for predicting ICI efficacy in patients with OSCC.

1. Introduction

In recent years, immune checkpoint inhibitors (ICIs) have emerged as a promising therapeutic agents for various cancer types, including oral squamous cell carcinoma (OSCC) [1]. Based on the results of Checkmate 141 trial and KEYNOTE-048 trial, ICIs is indicated as the first-line treatment for recurrent or metastatic head and neck cancer in the National Comprehensive Cancer Network (NCCN) guideline [2–4]. In Japan, for recurrent or metastatic head and neck cancer nivolumab was approved for administration in 2017, as well as pembrolizumab in 2019 [5]. ICIs work by blocking immune checkpoint proteins, such as programmed cell death protein 1 (PD-1) and its ligand (PD-L1), thereby enhancing the anti-tumor immune response [6]. While these agents have shown significant efficacy in some patients, they can also trigger diverse side effects known as immune-related adverse events (irAEs) [7]. These irAEs stem from increased immune activity and can impact multiple organ systems [7]. Several studies across different cancer types have suggested a potential link between irAEs and improved treatment outcomes with ICIs [8–10]. However, this relationship in OSCC remains unclear. This study aimed to investigate the association between the efficacy of ICIs and irAEs in patients with recurrent or metastatic OSCC to identify predictive factors for the efficacy of ICIs.

2. Materials and methods

2.1. Patient population

This retrospective study involved 40 patients with recurrent or

* 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).

https://doi.org/10.1016/j.ajoms.2025.09.015
Received 21 July 2025; Received in revised form 9 September 2025; Accepted 28 September 2025
Available online 2 October 2025

Please cite this article as: Kotaro Sakurai et al., *Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology*, https://doi.org/10.1016/j.ajoms.2025.09.015

metastatic OSCC who received ICIs as the first-line treatment at our department between April 2016 and September 2024. Data were reviewed retrospectively from medical records, including sex, age at the initial consultation, smoking history, primary tumor site, target lesion, combined positive score (CPS), TNM classification 8th edition [11], treatment regimen, number of ICI therapy cycles, treatment response, adverse events, prognosis, second-line treatment, and observation period. This study did not include patients with a history of hematopoietic stem cell transplantation or autoimmune disease. The medical history of the patients included was diabetes, arrhythmia, hypertension, hyperlipidemia, uterine fibroids, and spinal stenosis. The study was conducted following the Declaration of Helsinki guidelines and was approved by the Ethics Committee of our hospital (approval number: R2023016). Informed consent was waived using an opt-out approach due to the retrospective nature of this study.

2.2. Treatment protocol

Treatment selection followed the NCCN guidelines [2]. Nivolumab is indicated for platinum-resistant patients and pembrolizumab is indicated for platinum-sensitive patients; combination therapy with pembrolizumab plus chemotherapy is indicated if PD-L1 combined positive score (CPS) is less than 1, and single-agent or combination therapy is indicated if CPS is greater than 1 [5]. Platinum-resistant patients are those who experience recurrence or metastasis within 6 months after platinum administration, while platinum-sensitive patients experience it after 6 months [12]. Nivolumab was administered at a dosage of 240 mg every 2 weeks. Combination therapy consisted of Pembrolizumab at a dosage of 200 mg every 3 weeks, along with fluorouracil at a dosage of 1000 mg/m^2 (for 4 days) and cisplatin at a dosage of 100 mg/m^2 for up to six cycles, followed by a switch to Pembrolizumab monotherapy at a dosage of 200 mg every 3 weeks. In case of adverse events, such as irAEs, a dose reduction of fluorouracil and cisplatin was considered for grade 2, while grade 3 or higher events led to the postponement or withdrawal of treatment. When tumor control was no longer possible after ICI administration and the patient wished to receive subsequent treatment, salvage chemotherapy was scheduled. In the salvage chemotherapy, paclitaxel and cetuximab were administered weekly at doses of 80 and 400 mg/m^2, respectively, during the first cycle. During the second cycle and thereafter, the same doses of paclitaxel and 250 mg/m2 cetuximab were administered.

2.3. Evaluation

IrAEs were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) ver. 5.0 [13]. Treatment effects were assessed using Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 [14], with responses categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Outcome measures included overall response rate (ORR), disease control rate (DCR), overall survival (OS), and progression-free survival (PFS). Progression-free survival 2 (PFS 2) indicates the time from the start of primary treatment until disease progression after secondary treatment or death [15]. PFS 2 was also evaluated for patients who received subsequent therapy with cetuximab and paclitaxel after ICI administration.

2.4. Statistical analysis

For statistical analysis, the Mann–Whitney *U* test, Fisher's exact test and chi-square test were utilized to compare groups with and without irAEs. Survival analyses were conducted using the Kaplan–Meier method with the log-rank test or Gehan–Breslow–Wilcoxon test. Multivariate analysis was performed using a Cox proportional hazards model. Statistical significance was defined as $P < 0.05$. All statistical analyses were conducted using GraphPad Prism software (GraphPad Software, Boston, MA, USA).

3. Results

3.1. Patient Characteristics

Patient characteristics, including subsets of patients with (irAE+) and without (irAE-) irAEs, are summarized in Table 1. The study cohort comprised 19 (47.5 %) males and 21 (52.5 %) females, with a mean age of 70 years (range: 33–91 years). Smoking history, (namely, patients who have smoked in the past) was indicated in 15 (37.5 %) patients and nonsmoking in 25 (62.5 %) patients. The observation period varied from 1 to 70 months (median, 13.5 months). The primary sites included the tongue in 16 patients, the lower gingiva in 12 (30.0 %), the upper gingiva in six (15.0 %), the oral floor in 3 (7.5 %), the buccal mucosa in 2 (5.0 %), and the hard palate in 1 (2.5 %) patient. The target lesion was recurrent in 25 (62.5 %), metastatic in 12 (30.0 %), and both in 3 (7.5 %) patients. The CPS was 1 or less in 3 (7.5 %), 1–20 in 6 (15.0 %), 20 or more in 10 (25.0 %), and unknown (mostly in patients receiving nivolumab) in 21 (52.5 %). No significant difference between the irAE+ patients and irAE- patients ($P = 0.7$). The ICI regimen comprised nivolumab administered in 24 (60.0 %), pembrolizumab with fluorouracil and cisplatin administered in 10 (25.0 %), and pembrolizumab alone in six (15.0 %) patients. The mean number of ICIs administered was 12.9 (range: 1–68; median cycles: 5). The number of ICIs

Table 1
Patient characteristics (n = 40).

Characteristic	Entire cohort (n = 40)	irAE (n = 15)	No irAE (n = 25)	*P*
Age mean±SD	70 ± 12.4	67.7 ± 9.7	71.5 ± 13.8	0.2[a]
Sex				0.5[b]
Male	19 (47.5 %)	6 (40.0 %)	13 (52.0 %)	
Female	21 (52.5 %)	9 (60.0 %)	12 (48.0 %)	
Smoking history				0.5[b]
Smoking	15 (37.5 %)	7 (46.7 %)	8 (32.0 %)	
No-smoking	25 (62.5 %)	8 (53.3 %)	17 (68.0 %)	
Site of primary tumor				0.3[c]
Tongue	16 (40.0 %)	7 (46.7 %)	8 (32.0 %)	
Lower gingiva	12 (30.0 %)	4 (26.7 %)	8 (32.0 %)	
Upper gingiva	6 (15.0 %)	2 (13.3 %)	4 (16.0 %)	
Oral floor	3 (7.5 %)	2 (13.3 %)	0	
Buccal mucosa	2 (5.0 %)	0	3 (12.0 %)	
Hard palate	1 (2.5 %)	0	1 (4.0 %)	
Target legion				0.2[c]
Recurrence	25 (62.5 %)	7 (46.7 %)	18 (72.0 %)	
Metastasis	12 (30.0 %)	6 (40.0 %)	6 (24.0 %)	
Recurrence and metastasis	3 (7.5 %)	2 (13.3 %)	1 (4.0 %)	
Combined positive score				0.7[c]
< 1	3 (7.5 %)	2 (13.3 %)	1 (4.0 %)	
1 ~ 20	6 (15.0 %)	2 (13.3 %)	4 (16.0 %)	
20 <	10 (25.0 %)	4 (26.7 %)	6 (24.0 %)	
Unknown	21 (52.5 %)	7 (46.7 %)	14 (56.0 %)	
ICIs regimen				0.7[c]
Nivolumab	24 (60.0 %)	9 (60.0 %)	15 (60.0 %)	
Pembrolizumab+FP	10 (25.0 %)	3 (20.0 %)	7 (28.0 %)	
Pembrolizumab alone	6 (15.0 %)	3 (20.0 %)	3 (12.0 %)	
Cycle of ICIs mean±SD	12.9 ± 17.0	20.5 ± 22.3	8.3 ± 11.0	0.02[a]
Response to ICIs				0.02[c]
CR	10 (25.0 %)	7 (46.7 %)	3 (12.0 %)	
PR	7 (17.5 %)	3 (20.0 %)	4 (16.0 %)	
SD	9 (22.5 %)	4 (26.7 %)	5 (20.0 %)	
PD	14 (35.0 %)	1 (6.7 %)	13 (52.0 %)	
Second line treatment				
Salvage chemotherapy	12 (30.0 %)	6 (40.0 %)	6 (24.0 %)	0.2[b]
Best supportive care	11 (27.5 %)	2 (13.3 %)	9 (36.0 %)	

Abbreviation: irAE, immune-related adverse events; SD, standard deviation; ICIs, immune checkpoint inhibitors; FP, Fluorouracil and cisplatin; CR, complete response; PR, partial response; SD, stable disease; PD progressive disease

[a] Mann–Whitney *U* test,

[b] Fisher's exact test,

[c] chi-square test

administered was significantly higher in irAE+ patients compared to irAE- patients ($P < 0.05$). In second-line treatment, salvage chemotherapy, cetuximab, and paclitaxel were performed in 12 (30.0 %) patients, and best supportive care in 11 (27.5 %) patients.

3.2. Treatment Efficacy

The optimal response to ICIs included CR in 10 (25.0 %), PR in seven (17.5 %), SD in nine (22.5 %), and PD in 14 (35.0 %) patients, leading to an ORR of 42.5 % and a DCR of 65.0 % (Table 1).

In a subgroup analysis, irAE+ patients exhibited a significantly higher ORR of 66.7 % and DCR of 93.3 % compared to an ORR of 28.0 % and DCR of 48.0 % in irAE- patients, indicating a significant difference ($P < 0.05$ and < 0.01, respectively).

3.3. IrAEs

Twenty-two irAEs were observed in 15 patients (37.5 %), as summarized in Table 2. Grade 1/2 was observed in 14 patients (35.0 %) and Grade 3/4 in eight patients (20.0 %). The most prevalent irAE was thyroid dysfunction (n = 7, 17.5 %), followed by interstitial pneumonia (n = 3, 7.5 %) and adrenal insufficiency (n = 3, 7.5 %). Four patients (10.0 %) discontinued ICI treatment permanently due to arthritis, meningoencephalitis, myocarditis, or interstitial pneumonia. Multisystem irAEs occurred in 5 patients (12.5 %). Four of the five patients with multisystem irAEs achieved complete response, resulting in an ORR of 80 %. The 10 patients with single irAE had an ORR of 60 %. The response rates were compared using Fisher's exact test, no significant difference was observed ($P = 0.6$).

3.4. Survival outcomes

The median follow-up period was 15.5 months (interquartile range [IQR]: 6.3–35.3 months). The 5-year OS rate was 40.9 %, with a median OS of 15.5 months (IQR: 6–35 months).

In subgroup analysis, the 5-year OS rate was 65.0 % in the irAE+ patients, compared to 21.9 % in irAE- patients, exhibiting a significant difference (HR: 0.3; 95 % CI: 0.1–0.7; $P < 0.01$) (Fig. 1). The median OS was 36 months (IQR: 13–61 months) for irAE+ patients and 12 months (IQR: 5–19.5 months) for irAE- patients.

The 3-year PFS rate was 40.0 % in the irAE+ patients, whereas it was 29.3 % in irAE- patients, showing a significant difference (HR: 0.6; 95 % CI: 0.3–1.3; $P < 0.05$) (Fig. 2). The median PFS was 10 months (IQR: 4–55 months) for irAE+ patients and 2 months (IQR: 1–14 months) for irAE- patients.

Univariate analysis revealed significant prognostic factors for overall survival, including sex (male vs. female, hazard ratio [HR]: 2.8; 95 % Confidence Interval [CI]: 1.1–7.9; $P < 0.05$), cycles of ICIs (HR: 0.9; 95 % CI: 0.9–1.0; $P < 0.05$) and irAEs (HR: 0.2; 95 % CI: 0.059–0.61; $P < 0.01$) (Table 3). The independent variables included in the

Table 2
irAEs characteristics.

irAEs	Grade 1/2	Grade 3/4
Thyroid dysfunction	5 (12.5 %)	2 (5.0 %)
Interstitial pneumonia	3 (7.5 %)	
Dermatologic disorder	2 (5.0 %)	
Adrenal insufficiency	1 (2.5 %)	2 (5.0 %)
Pancreatitis	1 (2.5 %)	
Oral mucositis	1 (2.5 %)	
Arthritis	1 (2.5 %)	1 (2.5 %)
Meningoencephalitis		1 (2.5 %)
Myocarditis		1 (2.5 %)
Anemia		1 (2.5 %)
Total	14 (35.0 %)	8 (20.0 %)

Abbreviation: irAE, immune-related adverse events

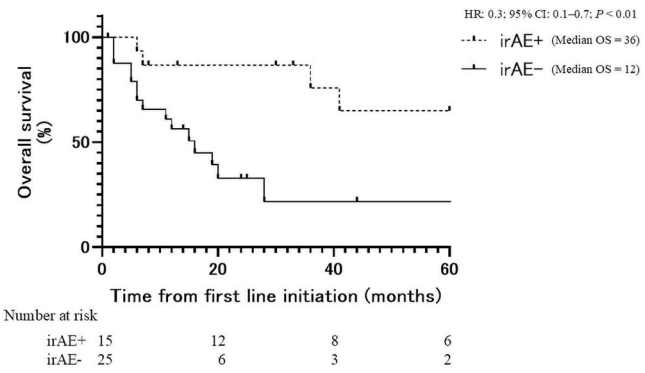

Fig. 1. Kaplan-Meier curves for OS divided by irAE occurrence Abbreviation: irAE, immune-related adverse events, OS, overall survival, HR, hazard ratio, CI, confidence interval. The 5-years OS rate was 65.0 % in irAE+ patients (n = 15), and 21.9 % in irAE- patients (n = 25), which was significantly different (HR: 0.3; 95 % CI: 0.1–0.7; $P < 0.01$). The median OS was 36 months for irAE+ patients and 12 months for irAE- patients.

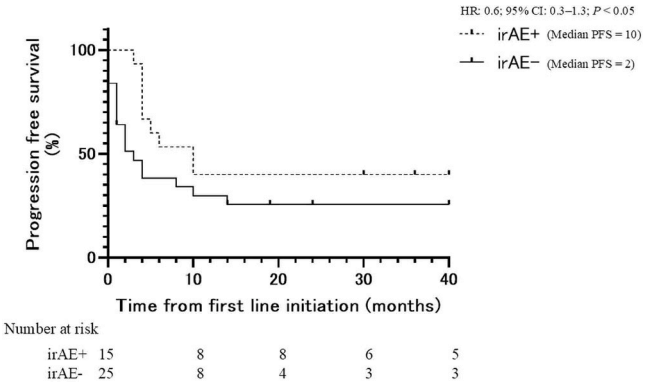

Fig. 2. Kaplan-Meier curves for PFS divided by irAE occurrence. Abbreviation: irAE, immune-related adverse events PFS, progression free survival, HR, hazard ratio, CI, confidence interval. The 3-years PFS rate was 40.0 % in irAE+ patients (n = 15), and 29.3 % in irAE- patients (n = 25), which was significantly different (HR: 0.6; 95 % CI: 0.3–1.3; $P < 0.05$). The median PFS was 10 months for irAE+ patients and 2 months for irAE- patients.

Table 3
Univariate and multivariate analysis for OS.

	Univariate analysis*			Multivariate analysis**		
Factor	HR	95 % CI	P value	HR	95 %CI	P value
Age	1.0	0.9 ~ 1.0	0.8			
Sex						
male vs female	2.8	1.1 ~ 7.9	0.04	2.3	0.9 ~ 6.6	0.1
ICIs type						
nivolumab vs pembrolizumab	0.5	0.2 ~ 1.4	0.2			
Cycle of ICIs	0.9	0.9 ~ 1.0	0.03	0.9	0.9 ~ 1.0	0.07
irAEs						
present vs absent	0.2	0.06 ~ 0.6	0.008	0.3	0.07 ~ 0.9	0.04
Smoking history						
no-smoking vs smoking	1.4	0.54 ~ 3.4	0.5			

Abbreviation: irAE, immune-related adverse events; ICIs, immune checkpoint inhibitors OS, overall survival, HR, hazard ratio, CI, confidence interval

* Fisher's exact test,

** Cox's hazard model

multivariate analysis were sex, cycles of ICIs, and irAEs. The Cox proportional hazards model identified irAEs (HR: 0.3; 95 % CI: 0.07–0.90; $P < 0.05$) as independent factors significantly associated with improved OS (Table 3). No significant factors for PFS were found in the univariate analysis.

Comparing single irAE+ patients (n = 10) and multisystem irAEs+ patients (n = 5), the 5-years OS rate was 90.0 % in single irAE+ patients, and 60.0 % in multisystem irAEs+ patients, which was not significantly different (HR: 0.6; 95 % CI: 0.1–4.1; $P = 0.5$) (Fig. 4). The median OS was 32 months (IQR: 12–62 months) for single irAE+ patients and 60 months (IQR: 22–61 months) for multisystem irAEs+ patients.

3.5. PFS 2 analysis

In patients who received subsequent therapy after ICIs (n = 12), irAE+ patients (n = 6) showed a tendency towards longer PFS 2 compared to irAE- patients (n = 6), namely, 1-year PFS2 rate was 83.3 % in the irAE+ patients compared to 33.3 % in irAE- patients, although this was not significant (HR: 0.2; 95 % CI: 0.03–1.4; $P = 0.1$) (Fig. 3). The median PFS 2 was 23 months (IQR: 7–61 months) for irAE+ patients and 7 months (IQR: 4–9 months) for irAE- patients.

4. Discussion

This study investigated the relationship between irAEs and efficacy of ICIs in patients with recurrent or metastatic OSCC. The analysis revealed a significantly higher ORR and DCR in irAE+ patients compared to irAE- patients. Multivariate analysis identified irAE occurrence and female sex as independent factors associated with prolonged OS. These findings suggest that irAE occurrence and female sex are linked to improved clinical outcomes.

As reported, patients who developed irAEs demonstrated enhanced efficacy compared to those without irAEs in various cancer types, including non-small cell lung cancer [16–19], melanoma [20], renal cell carcinoma [21,22], urothelial cancer [23,24], gastrointestinal cancer [25,26]and head and neck cancer [27,28]. In head and neck cancer, Pestana et al. reported an ORR of 42 % and a median OS of 8.4 months in head and neck cancer, regardless of irAEs occurrence [29]. Moreover, in a prior study on efficacy related to irAEs in head and neck cancer, irAE+ patients exhibited superior efficacy compared to irAE− patients [27]. Compared to these reports, this study showed higher efficacy in patients with irAEs. Furthermore, patients who received more ICIs had a significantly higher incidence of irAEs. This suggests that the number of

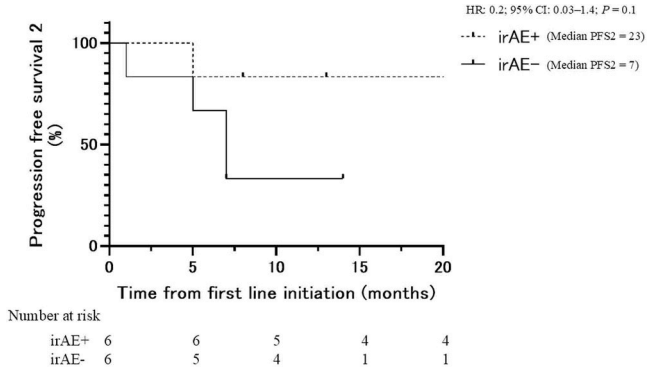

Fig. 3. Kaplan-Meier curves for PFS 2 divided by irAE occurrence. Abbreviation: irAE, immune-related adverse events PFS, progression free survival, HR, hazard ratio, CI, confidence interval. The 1-year PFS 2 rate was 83.3 % in irAE+ patients (n = 6), compared to 33.3 % in irAE- patients (n = 6), but this was not significantly different (HR: 0.2; 95 % CI: 0.03–1.4; $P = 0.1$). Median PFS 2 was 23 months for irAE+ patients and 7 months for irAE- patients.

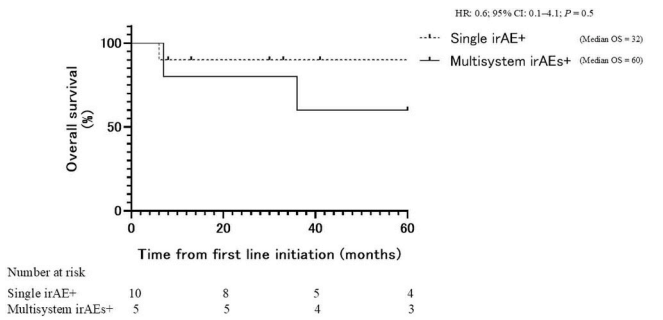

Fig. 4. Kaplan-Meier curves for OS divided by single irAE and multisystem irAEs occurrence. Abbreviation: irAE, immune-related adverse events, OS, overall survival, HR, hazard ratio, CI, confidence interval. The 5-years OS rate was 90.0 % in single irAE+ patients (n = 10), and 60.0 % in multisystem irAEs+ patients (n = 5), which was not significantly different (HR: 0.6; 95 % CI: 0.1–4.1; $P = 0.5$). The median OS was 32 months for single irAE+ patients and 60 months for multisystem irAEs+ patients.

ICI cycles may play a role in the development of irAEs.

The biological mechanisms underlying the antitumor effects and the development of irAEs need to be fully elucidated. One hypothesis is that irAEs reflects a generally enhanced immune response induced by ICIs, which may concurrently enhance anti-tumor immunity [30]. The development of irAEs may serve as a surrogate marker of baseline immunocompetence[7]. Baseline endogenous immune responses are required for antitumor effects and the development of T cell-driven irAEs [7]. The overlap between tumor-associated antigens and self-antigens could explain why an activated immune system targets both cancer cells and healthy tissues.

The incidence of irAEs was significantly higher in patients receiving a greater cycle of ICIs. However, multivariate analysis revealed that it was the occurrence of irAEs that contributed to prognosis, and the cycles of ICIs was not an independent factor. This is likely because patients with longer survival times have more opportunities to receive ICIs, making them more susceptible to developing irAEs during this process, which is why the cycles of ICIs appeared to be associated with a better prognosis in univariate analysis. However, in multivariate analysis, irAEs occurrence was independently associated with prognosis, and the effect of the cycles of ICIs disappeared. These results support the idea that irAEs are a biological indicator of ICI-induced immune activation and may more directly reflect treatment efficacy and prognosis.

In this study, in addition to cycles of ICIs and irAEs, the female sex was included in the multivariate analysis as an independent variable associated with improved OS. Endocrine irAEs have a higher occurrence in females [31]. Several studies have reported sex-based differences in irAE incidence, particularly in endocrine-related complications [8]. Additionally, patients experiencing irAEs that affect the skin, endocrine glands, or gastrointestinal tract exhibit better survival outcomes [32]. In this study, among the 11 patients with skin or endocrine irAEs, eight were females, demonstrating notably high ORR (72.0 %) and DCR (100.0 %). However, the impact of sex on ICI efficacy remains controversial and requires further investigation to elucidate the underlying mechanisms.

Regarding multisystem irAEs, a meta-analysis of non-small cell lung cancer has reported that higher efficacy was observed in patients with multisystem irAEs [33]. Although no significant difference was observed in this study, further investigation is needed to accumulate more cases.

In this study, regarding later salvage chemotherapy, no significant outcomes were noted, regardless of the presence of irAEs due to insufficient number of cases and duration of observation. However, salvage chemotherapy following the administration of ICIs may extend OS, particularly cetuximab and paclitaxel [34]. Additional research with sufficient sample sizes and extended follow-up durations is necessary.

To the best of our knowledge, only two studies have been reported in

head and neck cancer, and this study is the first in oral cancer, providing important evidence. However, this study had several limitations, including its retrospective nature, single-center design, short follow-up period, and relatively small sample size. Furthermore, heterogeneity in ICI regimens (monotherapy vs. combination therapy) may have influenced the outcomes. Owing to this investigation being a preliminary study, accumulation of cases and larger prospective studies are required to validate these findings and explore potential predictive biomarkers for irAE occurrence and ICI efficacy.

5. Conclusion

The present study suggests that the occurrence of irAEs amplified the efficacy of ICI in oral cancer. A significant association between the occurrence of irAEs and improved clinical outcomes in patients with OSCC treated with ICIs has been identified. Future research should focus on elucidating the mechanisms underlying this association and on developing strategies to balance ICI efficacy with the risk of irAEs.

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