Sequential immune checkpoint inhibition after palliative radiotherapy in patients with advanced head and neck squamous cell carcinoma: A retrospective cohort study

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Abstract. Head and neck squamous cell carcinoma (HNSCC) frequently presents at an advanced stage, where curative options are often not feasible. Palliative radiotherapy (RT) can relieve symptoms and improve performance status, potentially enabling systemic therapy. Immune checkpoint inhibitors (ICIs) have a survival benefit in recurrent and metastatic HNSCC; however, the optimal sequencing of RT and ICIs remains to be elucidated. The present study aimed to evaluate the clinical outcomes of ICI therapy administered after palliative RT in patients with advanced HNSCC. Consecutive patients with advanced HNSCC treated at The University of Tokyo Hospital (Tokyo, Japan) between January 2017 and December 2024 were retrospectively reviewed. Eligible patients received initial palliative RT, with or without subsequent ICIs within 6 months (RT-ICI vs. RT groups). Clinical data, including demographics, RT parameters, treatment regimens and outcomes, were collected. Overall survival (OS) and progression-free survival (PFS) analyses were performed using the Kaplan-Meier method and Cox proportional hazards models. Among 74 patients (median age, 75 years; 82% male), 17 received ICIs following RT. The RT-ICI group achieved a 2-year OS rate of 55.8% compared with 5.7% in the RT group (P<0.001). Median PFS time in the RT-ICI group was 12.7 months, with a 2-year PFS rate of 20.9%. Multivariate analysis confirmed RT-ICI treatment [hazard ratio (HR) 0.22, 95% confidence interval (CI) 0.09-0.55; P=0.001], higher biologically effective dose (≥39 Gy; HR 0.46, 95% CI 0.24-0.91; P=0.025) and preserved performance status (HR 1.99, 95% CI 1.02-3.88; P=0.043) as independent predictors of OS. Grade 3 or higher immune-related adverse events occurred in three patients (17.6%). In conclusion, sequential ICI therapy after palliative RT was revealed to be associated with improved survival outcomes in patients with advanced HNSCC. Higher RT dose was also associated with a better survival; however, no causal or mechanistic conclusions can be drawn from this observation. Further prospective studies are warranted to confirm these findings, and to clarify the optimal sequencing and dosing strategies.

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is a heterogeneous malignancy with a substantial global burden, accounting for approximately 890 thousand new cases and 450 thousand deaths annually (1). Prognosis is influenced by the clinical stage, with up to 60% of patients being diagnosed at a locally advanced stage (2). While curative-intent treatment remains feasible for these patients, a significant proportion are deemed ineligible due to advanced age, comorbidities, or impaired renal function (3). For patients who cannot undergo definitive therapy, palliative radiotherapy (RT) remains an important treatment option, providing rapid symptom relief such as pain, bleeding, dysphagia, and airway compromise. In selected cases, palliative RT can also achieve meaningful local tumor control, which may improve performance status, facilitate subsequent systemic therapy, and contribute to the preservation of quality of life (4-6).

Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis have been used to treat unresectable, recurrent, or metastatic HNSCC. The pivotal CheckMate-141 and KEYNOTE-048 trials demonstrated the survival benefits of nivolumab and pembrolizumab, respectively, establishing ICIs as standard systemic therapies in appropriate patients (7,8). However, the optimal sequencing of ICIs using RT in routine practice remains unclear. In locally advanced disease, two phase III trials evaluating the concurrent addition of ICIs to definitive chemoradiotherapy (CRT) reported negative results: KEYNOTE-412, which tested pembrolizumab plus CRT (9), and JAVELIN Head and Neck 100, which tested avelumab plus CRT (10). A recent phase II randomized trial

by Zandberg *et al* (11) compared concurrent vs. sequential pembrolizumab with CRT, and found that the sequential strategy was associated with superior clinical outcomes compared to the concurrent approach. In parallel, the development of reliable biomarkers to identify patients most likely to benefit from ICIs remains a critical unmet need.

Present study uniquely evaluates a real-world sequential strategy of palliative radiotherapy followed by immune checkpoint inhibition in patients with advanced HNSCC. In addition, we examine the prognostic impact of radiotherapy dose intensity using the biologically effective dose. Accordingly, we conducted a retrospective cohort study to assess overall survival, progression-free survival, and treatment-related toxicity.

Materials and methods

Patients. This retrospective study included consecutive patients with advanced head and neck squamous cell carcinoma who underwent palliative radiotherapy as the initial oncologic treatment at The University of Tokyo Hospital (Tokyo, Japan) between January 2017 and December 2024. Eligible patients met the following inclusion criteria: i) Pathologically confirmed head and neck squamous cell carcinoma; ii) advanced-stage disease according to the American Joint Committee on Cancer (AJCC) 8th edition (stages III-IVC); iii) no prior oncologic treatment for the index cancer; and iv) initiation of palliative radiotherapy to the head and neck region. Patients were excluded if they had another active malignancy at the time of radiotherapy or if clinical records were insufficient to assess treatment exposure or survival outcomes. All patients received palliative radiotherapy at study entry and were subsequently classified into two groups according to post-radiotherapy management: patients who did not receive immune checkpoint inhibitors (RT group) and patients who received immune checkpoint inhibitors within six months after radiotherapy initiation (RT-ICI group).

Treatment methods. Radiotherapy techniques included intensity-modulated radiotherapy or three-dimensional conformal radiotherapy, selected at the discretion of the treating radiation oncologist. All patients underwent computed tomography (CT) in the supine position with thermoplastic mask immobilization, in accordance with our institutional protocol (12). Contrast-enhanced CT scans were acquired from the vertex to the clavicle and were transferred to a treatment planning system. Target volumes and organs at risk (OARs) were delineated according to the institutional guidelines. The gross tumor volume (GTV) was defined as the visible tumor on imaging. The clinical target volume (CTV) was set to be identical to the GTV. The planning target volume (PTV) was created by adding a 3-5 mm margin to the CTV. No prophylactic irradiation was performed. A radiation oncologist determined the dose and fractionation at the time of therapy. The biologically effective dose (BED_{10}) was calculated by assuming an α/β ratio of 10.

Radiotherapy planning was optimized using dose-volume histogram analyses to ensure adequate target coverage while minimizing OAR exposure. Adjuvant ICI therapy, primarily pembrolizumab or nivolumab, was administered intravenously in accordance with standard institutional protocols. The ICI regimens included pembrolizumab at a fixed dose of 200 mg per body every 3 weeks, with a 6-weekly dose of 400 mg per body permitted after more than 1 year of treatment, or a combination chemotherapy regimen (CF-PEM) consisting of pembrolizumab 200 mg per body on day 1, cisplatin 80 mg/m^2 on day 1, and 5-fluorouracil 800 mg/m^2 on days 1-5.

Data collection and outcome measures. Clinical data, including patient demographics, tumor characteristics, radiotherapy details (total dose and fractionation scheme), type and duration of ICI therapy, and follow-up information, were retrospectively collected from electronic medical records. The Karnofsky Performance Status (KPS) was documented before the initiation of radiotherapy. The clinical outcomes included overall survival (OS), progression-free survival (PFS), and treatment-related adverse events, which were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. OS and PFS were defined from the date of radiotherapy initiation to death or progression, respectively, or to the date of the last follow-up for censored cases. Survival curves for OS and PFS were estimated using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test. Patients without documented events were censored at the date of last clinical follow-up. Cox proportional hazards regression models were applied for multivariable analyses to identify factors significantly associated with OS, with adjustment for clinically relevant covariates. Propensity score matching (PSM) was considered to further address potential confounding; however, given the limited sample size, particularly in the RT-ICI group, PSM was deemed statistically inefficient and likely to result in substantial loss of information. Therefore, multivariable Cox regression was adopted as the primary method for confounder adjustment. Statistical significance was set at $P<0.05$. All statistical analyses were performed using the R software (version 4.3.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

The baseline characteristics of the patients are summarized in Table I. The cohort comprised 74 patients with a median age of 75 years (range, 51-98 years); 61 (82.4%) were male. Performance status was generally preserved, with a median KPS of 80, and 61% of patients had a KPS ≥80. The primary tumor sites were the oral cavity (31.1%), hypopharynx (29.7%), oropharynx (20.3%), and other sites (18.9%). The disease burden was largely advanced, with T4a-c in 86.5% of patients and T3 in 13.5%. The median prescribed dose was 30 Gy (range, 8-39 Gy), the median number of fractions was 10 (range, 1-13), and the median BED_{10} was 39.0 Gy (range, 11.2-50.7 Gy).

Seventeen patients received ICIs after palliative radiotherapy (RT-ICI group). Of these, 15 received pembrolizumab monotherapy and two received cisplatin/5-fluorouracil plus pembrolizumab (CF-PEM). Among the patients in the 17 RT-ICI group, 11 (73.3%) had a Combined Positive Score (CPS) ≥20, 4 (26.7%) had CPS 1-19, and none had CPS 0; CPS was not assessed in two patients (11.8%). The median number of ICI administration cycles was nine (range, 2-27). The remaining 57 patients comprised the RT group without ICI; of these,

Table I. Baseline patient characteristics (n=74).

Variable	Value
Median age, years (range)	75 (51-98)
Sex, n (%)	
Male	61 (82.4%)
Female	13 (17.6%)
Karnofsky performance status, n (%)	
90	13 (17.6%)
80	32 (43.2%)
70	16 (21.6%)
60	8 (10.8%)
50	3 (4.1%)
40	2 (2.7%)
Primary tumor location, n (%)	
Oral cavity	23 (31.1%)
Hypopharynx	22 (29.7%)
Oropharynx	15 (20.3%)
Larynx	4 (5.4%)
Paranasal sinus	4 (5.4%)
Nasal cavity	3 (4.1%)
Nasopharynx	2 (2.7%)
External auditory canal	1 (1.4%)
Clinical stage, n (%)	
III	10 (13.5%)
IVA	25 (33.8%)
IVB	20 (27.0%)
IVC	19 (25.7%)
Median prescribed dose, Gy (range)	30 (8-39)
Median fractionation, fractions (range)	10 (1-13)
Median biologically effective dose[a], Gy (range)	39.0 (11.2-50.7)

[a]α/β ratio: 10.

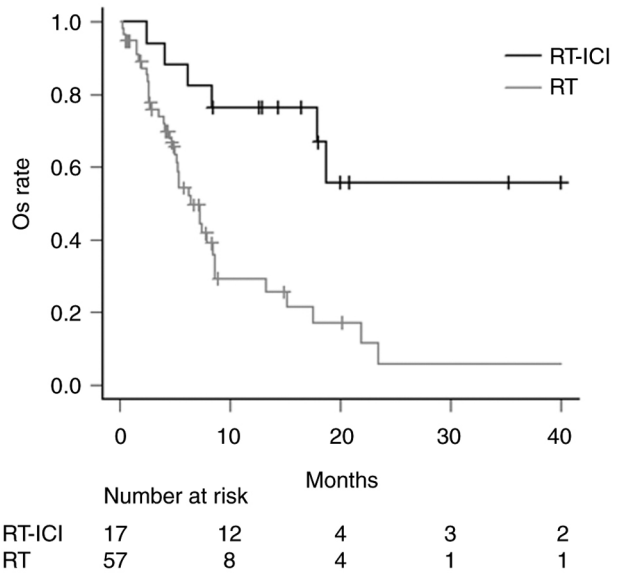

Figure 1. Kaplan-Meier curves for OS comparing RT-ICI (n=17) with RT (n=57). Tick marks indicate censored observations, and numbers at risk are shown below the x-axis. Group comparisons by the log-rank test showed a longer OS in the RT-ICI group (P<0.001). ICI, immune checkpoint inhibitor; OS, overall survival; RT, radiotherapy.

six subsequently received chemotherapy after radiotherapy (oral S-1 in three patients and cisplatin/5-fluorouracil plus cetuximab in three).

The median follow-up was 6.2 months (range, 0.3-51.8). A significant difference in OS was observed between the RT-ICI and RT groups (P<0.001). The 6-month, 1-year, and 2-year OS rates were 88.2% 76.5, and 55.8% in the RT-ICI group, compared with 54.3, 29.2, and 5.7% in the RT group, respectively (Fig. 1). The PFS rate in the RT-ICI group were 76.5% at 6 months, 52.3% at 1 year, and 20.9% at 2 years. Among the 17 patients in the RT-ICI group, 10 discontinued treatments due to disease progression during the study period (Fig. 2). Post-progression management included systemic therapy in five patients (paclitaxel plus cetuximab in four and pemigatinib in one), local therapy in two patients (BNCT or TPL), and best supportive care in three patients. Three patients discontinued ICI due to grade ≥3 immune-related adverse events (irAEs), specifically grade 4 hepatitis, grade 3 cytokine-release syndrome, and grade 3 adrenal insufficiency. Two patients experienced grade 3 mucositis as adverse events related to palliative radiotherapy.

In univariate analysis, RT-ICI treatment [hazard ratio (HR), 0.23; 95% confidence interval (CI), 0.10-0.56; P=0.001], a BED_{10} ≥39 Gy (HR, 0.44; 95% CI, 0.23-0.85; P=0.015), and better performance status (HR, 2.02; 95% CI, 1.09-3.73; P=0.025) were significantly associated with OS (Table II). In multivariate analysis, performance status (HR, 1.99; 95% CI, 1.02-3.88; P=0.043), RT-ICI treatment (HR, 0.22; 95% CI, 0.09-0.55; P=0.001), and a BED_{10} ≥39 Gy (HR, 0.46; 95% CI, 0.24-0.91; P=0.025) remained independent prognostic factors.

Discussion

Our study demonstrated that the addition of ICI therapy following palliative radiotherapy resulted in favorable and durable outcomes, with a 2-year OS of 55.8% and 2-year PFS of 20.9% in patients with advanced HNSCC. These results compare favorably with previously reported outcomes for palliative radiotherapy alone, in which median survival ranged from 7 to 11 months in similar cohorts (13,14).

According to the updated results of the Phase III KEYNOTE-048 study, with a median follow-up of 45 months, pembrolizumab monotherapy achieved a median OS of 11.6 months, while pembrolizumab combined with chemotherapy achieved a median OS of 13.6 months in the overall cohort (15). Two-year OS rates remained at approximately 20-30% with pembrolizumab-based regimens, although differences in patient selection, disease stage, and treatment intent should be considered. Collectively, these findings support the idea that radiotherapy may potentiate the efficacy of ICIs through immunogenic modulation, thereby leading to durable survival benefits. In line with this, Cheng *et al* (16) reported in a retrospective study of 113 patients with recur-

Table II. Univariate and multivariate Cox regression analyses for overall survival.

Covariable	Univariate hazard ratio (95% CI)	Univariate P-value	Multivariate hazard ratio (95% CI)	Multivariate P-value
Age				
≤75 (reference) vs. >75 years	1.121 (0.614-2.047)	0.710	1.754 (0.832-3.698)	0.140
Sex				
Male (reference) vs. Female	1.166 (0.513-2.649)	0.713	0.939 (0.378-2.333)	0.892
Karnofsky performance status				
80-100 (reference) vs. ≤70	2.018 (1.092-3.731)	0.025	1.991 (1.022-3.879)	**0.043**
Distant metastasis				
No (reference) vs. Yes	1.189 (0.598-2.365)	0.621	1.543 (0.712-3.345)	0.272
Treatment modality				
RT (reference) vs. RT-ICI	0.233 (0.097-0.560)	0.001	0.221 (0.090-0.546)	**0.001**
Biologically effective dose				
<39 (reference) vs. ≥ 39 Gy	0.441 (0.229-0.853)	0.015	0.464 (0.237-0.907)	**0.025**

CI, confidence interval; HR, hazard ratio. Bold values indicate statistical significance (P<0.05).

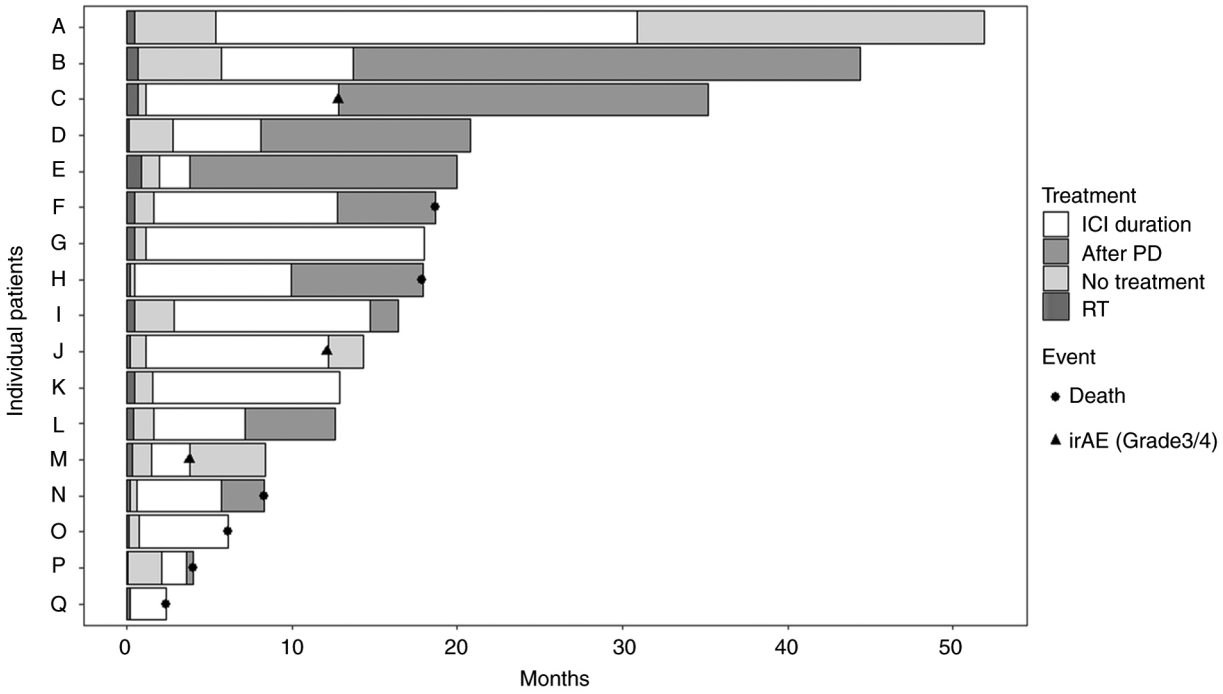

Figure 2. Swimmer plot of patient-level courses in the RT-ICI cohort (n=17). Bars depict individual timelines from the start of radiotherapy (Time 0). Segments indicate treatment phases: Radiotherapy, periods without systemic therapy, ICI duration and management after radiographic/clinical progression. Patients were ordered by total follow-up. Symbols mark key events. The x-axis represents the months from the start of RT. ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PD, progressive disease; RT, radiotherapy.

rent or metastatic HNSCC that the addition of radiotherapy to immunotherapy significantly improved outcomes, with higher response rates (ORR 67.6% vs. 39.5%) and prolonged survival (median PFS 20.0 vs. 4.0 months; median OS not reached vs. 26.0 months) compared with immunotherapy alone.

The synergistic potential of radiotherapy and ICIs is supported by preclinical evidence. Ionizing radiation induces tumor cell death and enhances tumor antigen release and presentation by antigen-presenting cells, thereby promoting peripheral T cell priming with cell lines of breast cancer *in vitro* and *in vivo* (17). This process augments the efficacy of ICIs such as PD-1/PD-L1 blockade by facilitating T cell reactivation (18). In addition, radiotherapy can modulate the tumor microenvironment by increasing vascular permeability and chemokine production and promoting immune cell infiltration into the tumor (19-21). Consequently, a hot tumor

microenvironment enhances responsiveness to ICIs and fosters therapeutic synergy (22-24).

The clinical efficacy of ICI administration after radiotherapy has been clearly demonstrated in other malignancies, particularly lung cancer. The PACIFIC trial demonstrated that consolidation therapy with durvalumab, an anti-PD-L1 monoclonal antibody, following chemoradiotherapy significantly improved outcomes in stage III non-small-cell lung cancer. The 5-year OS rate was 42.9% with durvalumab vs. 33.4% with a placebo, confirming that a durable survival benefit was maintained beyond 5 years (25). The ADRIATIC trial in limited-stage small-cell lung cancer showed that durvalumab consolidation after chemoradiotherapy prolonged both PFS and OS compared to placebo (26). Our findings are consistent with these observations. Further studies are warranted to clarify the optimal sequencing of radiotherapy and immune checkpoint inhibition. Given the retrospective, single-institution nature of the present study, prospective randomized trials are needed to formally evaluate different RT-ICI sequencing strategies. In addition, optimization of treatment timing should be explored, as the efficacy of ICIs may vary according to their class and the temporal relationship with radiotherapy. Finally, mechanistic investigations incorporating translational biomarkers and advanced imaging approaches are required to elucidate how radiotherapy modulates the tumor microenvironment and immune responsiveness, thereby informing rational integration of RT and ICIs in future clinical practice.

In the present study, a higher radiation dose (BED_{10} ≥39 Gy) was independently associated with improved survival outcomes, suggesting a possible dose-response relationship even in the palliative setting. However, the potential survival benefit of dose escalation must be carefully weighed against the risk of treatment-related toxicity, particularly in palliative patients for whom symptom control and quality of life are primary treatment goals. Higher-dose radiotherapy has been proposed to enhance antitumor immune responses through increased tumor antigen release and immune activation, which may augment the efficacy of immune checkpoint inhibitors (27). Supporting this concept, a meta-analysis by Viani *et al* (28), including 28 studies and 1,986 patients, reported that higher dose was associated with superior overall response rates and an improved therapeutic ratio. Stereotactic body radiation therapy (SBRT), a novel technique that enables highly concentrated dose delivery to the target while sparing surrounding normal tissues, represents a promising strategy (29,30). Its clinical value is currently being evaluated in a phase III randomized trial comparing SBRT with conventional palliative radiotherapy for painful bone metastases (NCT06065449).

However, the optimal dose and fractionation schedule for palliative RT in the context of sequential RT-ICI therapy remains uncertain. Dose escalation must be carefully balanced against treatment-related toxicity, particularly mucositis, xerostomia, and swallowing dysfunction, which can substantially affect quality of life in patients with advanced head and neck cancer. Notably, a phase III randomized trial in patients unsuitable for curative treatment demonstrated no significant differences in OS or PFS between 20 Gy in five fractions and a dose-escalated 30 Gy in five fractions regimen, with comparable toxicity profiles, suggesting that moderate dose escalation may be feasible but not necessarily associated with clear survival benefit (31).

Despite its retrospective nature, this analysis was conducted at a single institution with relatively consistent clinical practices regarding radiotherapy planning and immune checkpoint inhibitor administration. Nevertheless, several important limitations should be acknowledged. First, the retrospective design is inherently subject to selection bias, which may have influenced treatment allocation and could have resulted in an overestimation of survival outcomes, thereby limiting the generalizability of the findings. In particular, the comparison between the RT-ICI and RT-alone groups is susceptible to immortal time bias, as patients in the RT-ICI group must, by definition, have survived long enough to receive subsequent immunotherapy. In the absence of formal time-dependent statistical adjustments, such as a landmark analysis, the observed survival differences should therefore be interpreted with caution and cannot be considered fully causal. Second, the median follow-up period was relatively short, and long-term survival estimates were based on a limited number of patients at risk, as reflected by the wide confidence intervals; accordingly, greater emphasis should be placed on earlier endpoints. Third, the small sample size, particularly in the RT-ICI cohort, limits statistical power and may affect the robustness of the observed associations. In addition, key biological variables relevant to immunotherapy response, such as PD-L1 combined positive score (CPS), were not available for all patients. Given the incomplete availability of CPS data and the limited number of evaluable cases, we were unable to reliably assess the interaction between PD-L1 status, radiotherapy dose intensity, and survival outcomes, either through subgroup analyses or inclusion as covariates in multivariable models. This limitation may have constrained our ability to elucidate potential effect modification by tumor immunophenotype and should be considered when interpreting the observed survival benefits. Furthermore, the study population was predominantly male, elderly, and had relatively preserved performance status, which limits extrapolation of the findings to younger patients, female patients, or more frail subgroups, including those with poor performance status or very advanced age. Finally, although radiotherapy planning and delivery were performed according to standardized institutional protocols, some degree of heterogeneity in radiotherapy techniques and dose-fractionation schedules remained across patients; this residual variability may have influenced outcome interpretation and limits reproducibility. Prospective studies with larger cohorts, comprehensive biomarker profiling, and appropriate time-dependent analyses are warranted to better define the optimal radiotherapy dose intensity, including relevant thresholds, as well as the timing and sequencing of ICI administration.

In conclusion, in patients with advanced HNSCC, ICI given within 6 months after palliative RT was associated with better OS and PFS. Higher radiation dose was also associated with better outcomes; however, these findings should be interpreted as associations rather than evidence of a causal effect. Prospective studies with appropriate time-dependent analyses are needed to confirm these results and to guide the integration of RT and ICI in advanced head and neck cancer.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AK was a major contributor to writing this manuscript, and collected and assembled the data. AK and HY analyzed and interpreted the clinical data. YS conceived of this study, and participated in its design and coordination. AO and MM made substantial contributions to data curation and interpretation of data. YI, KY, KK and YS contributed to the acquisition of clinical data. AO, MM, YI, KY, KK, HY and YS revised the manuscript critically for important intellectual content. AK and HY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the ethical principles outlined in The Declaration of Helsinki. The study was approved by the Research Ethics Committee of the Faculty of Medicine of the University of Tokyo (IRB no. 3372-7; Tokyo, Japan). The requirement for informed consent was waived due to the retrospective design of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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