RESEARCH LETTER

Comparison of Adjuvant and Salvage Therapy with Immune Checkpoint Inhibitors in Head and Neck Mucosal Melanoma Treated with Proton Beam Therapy: A Retrospective Cohort Study

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To the Editor,

Mucosal melanoma (MM) of the head and neck (MMHN) without distant metastases is often an anatomically inoperable lesion, and radiation therapy, including proton beam therapy (PBT), may be the first choice of treatment instead of surgery. However, few studies have examined whether adjuvant therapy with immune checkpoint inhibitors (ICIs) should be administered after completion of any radiotherapy in MMHN. We compared the prognostic value of adjuvant ICI therapy with PBT and salvage ICI therapy after tumour progression in patients with MMHN undergoing PBT.

This study, undertaken at Shizuoka Cancer Center from August 2004 to December 2024, involved 31 patients who were histologically diagnosed with MMHN and underwent PBT at our hospital. The adjuvant ICI group included patients in whom ICI was initiated concurrently with PBT or after completion of PBT. The salvage ICI group included patients who received no follow-up treatment or adjuvant therapy with cytotoxic anticancer agents after PBT and received ICI after tumour progression. The PBT procedure was performed according to the high-dose PBT protocol previously published by our hospital (1). ICI regimens included nivolumab or pembrolizumab monotherapy (PD-1) and a combination of nivolumab and ipilimumab (NIVO+IPI). The primary outcomes were progression-free survival (PFS) and overall survival (OS) from the start of PBT. Baseline characteristics were compared using the Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. Survival curves were generated using the Kaplan–Meier method, and differences in survival were assessed using the log-rank test.

The baseline characteristics of the 31 patients with MMHN are presented in **Table I**. The salvage group received significantly higher doses of PBT than the adjuvant group ($p=0.023$). In the adjuvant group, 9 patients received PD-1 and 1 received NIVO+IPI as adjuvant therapy. In the salvage group, 9 patients received adjuvant therapy with a cytotoxic anticancer agent other than ICI with PBT, and after tumour progression, 20 patients received PD-1 and 1 received NIVO+IPI. There was no significant difference in PFS between the 2 groups (median PFS: 6.8 vs 11.5 months, $p=0.788$) (**Fig. 1**A). There was no statistically significant difference in OS, although OS tended to be better in the salvage group (median OS: 13.6 vs 42.0 months, $p=0.217$) (Fig. 1B).

Table I. Clinical and demographic characteristics of 31 patients with head and neck mucosal melanoma

Attribute	Patient group			*p*-value
	Total	Adjuvant ICI	Salvage ICI	
Patients, *n* (%)	31 (100.0)	10 (32.3)	21 (67.7)	
Age, median [range]	74.0 [51.0, 86.0]	70.0 [63.0, 84.0]	76.0 [51.0, 86.0]	
Sex, *n* (%)				1.000
Male	11 (35.5)	3 (30.0)	8 (38.1)	
Female	20 (64.5)	7 (70.0)	13 (61.9)	
ECOG-PS score, *n* (%)				1.000
0	29 (93.5)	10 (100.0)	19 (90.5)	
1	2 (6.5)	0 (0.0)	2 (9.5)	
Primary site, *n* (%)				0.077
Nasal cavity	26 (83.9)	8 (80.0)	18 (85.7)	
Paranasal cavity	2 (6.5)	2 (20.0)	0 (0.0)	
Oral cavity	3 (9.7)	0 (0.0)	3 (14.3)	
Clinical stage, *n* (%)				0.474
III	4 (12.9)	0 (0.0)	4 (19.0)	
IVA	26 (83.9)	10 (100.0)	16 (76.2)	
IVB	1 (3.2)	0 (0.0)	1 (4.8)	
T classification, *n* (%)				0.574
T3	7 (22.6)	1 (10.0)	6 (28.6)	
T4a	23 (74.2)	9 (90.0)	14 (66.7)	
T4b	1 (3.2)	0 (0.0)	1 (4.8)	
N classification, *n* (%)				
N0	26 (83.9)	8 (80.0)	18 (85.7)	1.000
N1	5 (16.1)	2 (20.0)	3 (14.3)	
BRAF mutation, *n* (%)				0.458
Not investigated	16 (51.6)	4 (40.0)	12 (57.1)	
Negative	15 (48.4)	6 (60.0)	9 (42.9)	
Positive	0 (0.0)	0 (0.0)	0 (0.0)	
LDH value, *n* (%)				0.652
≥ ULN	7 (22.6)	3 (30.0)	4 (19.0)	
< ULN	24 (77.4)	7 (70.0)	17 (81.0)	
NLR, median [range]	2.24 [1.06, 18.80]	2.16 [1.06, 10.32]	2.41 [1.23, 18.80]	
Postoperative recurrence, *n* (%)				0.296
Yes	26 (83.9)	3 (30.0)	2 (9.5)	
No	5 (16.1)	7 (70.0)	19 (90.5)	
PBT, *n* (%)				**0.023**
60 Gy/15 Fr	15 (48.4)	8 (80.0)	7 (33.3)	
70 Gy/20 Fr	16 (51.6)	2 (20.0)	14 (66.7)	
Tumour response after PBT, *n* (%)				1.000
Disappearance	18 (58.1)	6 (60.0)	12 (57.1)	
Residual	13 (41.9)	4 (40.0)	9 (42.9)	

ECOG-PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; NLR: neutrophil-to-lymphocyte ratio; PBT: proton beam therapy; ULN: upper limit of normal. Items in bold indicate statistically significant differences: $p<0.05$.

There are no large clinical trials specific to MMHN due to its rarity, and most treatment strategies follow those for cutaneous melanoma (CM). However, many studies have shown that the biological characteristics of MM differ from those of CM, and that it may not be appropriate to apply the same treatment strategies to both diseases. Regarding adjuvant immunotherapy in MM, Jacques et al. reported on 55 patients with MM and found no significant differences in recurrence-free survival (RFS) ($p=0.3799$), distant metastasis-free survival (DMFS) ($p=0.1150$), or

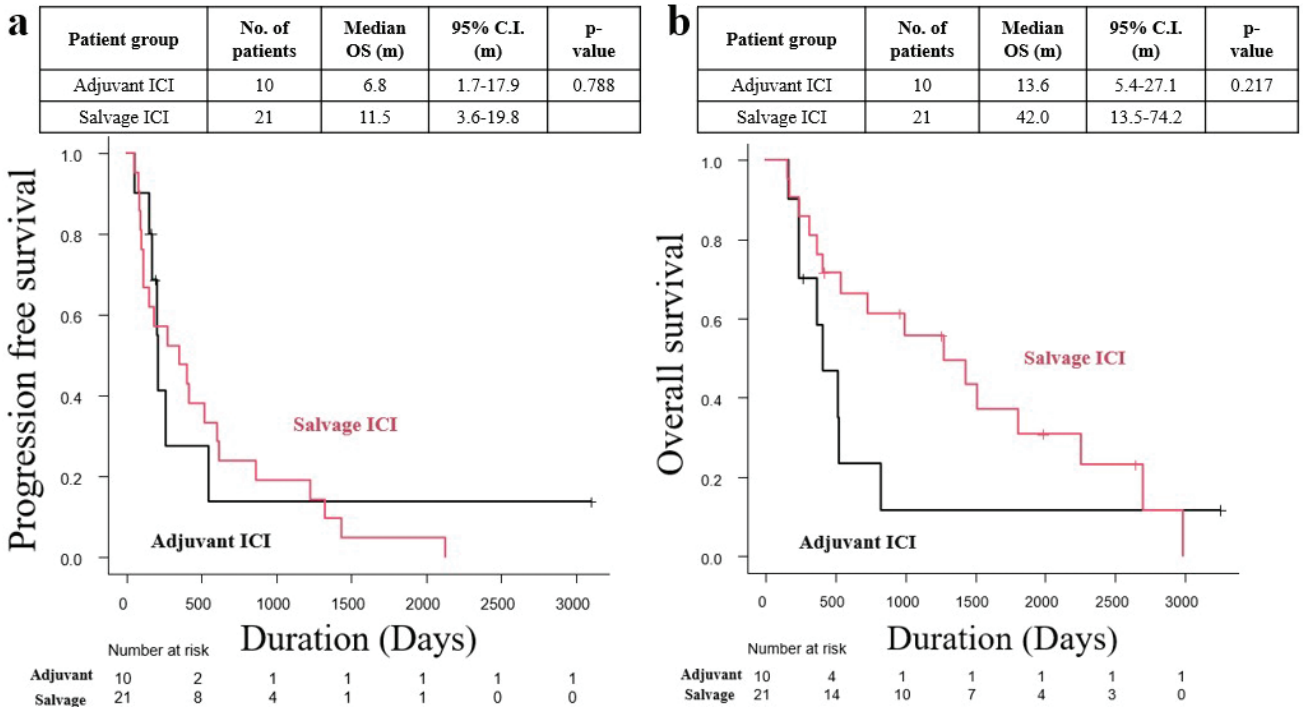

Fig. 1. Comparison of progression-free survival (PFS) and overall survival (OS) between the adjuvant ICI and salvage ICI groups. (A) Kaplan–Meier analysis of PFS with a univariate log-rank test. No significant difference in PFS was observed between the 2 groups (median PFS: 6.8 vs 11.5 months; $p=0.788$). The 1-, 2-, and 3-year PFS rates were 27.4% vs 47.6%, 13.7% vs 23.8%, and 13.7% vs 19.0%, respectively (adjuvant vs salvage). (B) Kaplan–Meier analysis of OS with a univariate log-rank test. Although the difference in OS was not statistically significant, a trend toward improved OS was noted in the salvage group compared with the adjuvant group (mean OS: 13.6 vs 42.0 months; $p=0.217$). The 1-, 2-, and 3-year OS rates were 77.8% vs 81.0%, 25.9% vs 66.3%, and 13.0% vs 55.7%, respectively (adjuvant vs salvage).

OS ($p=0.8366$) between patients who received adjuvant PD-1 therapy and those who did not (2). Furthermore, Lian et al. compared the efficacy of cisplatin plus temozolomide chemotherapy with toripalimab (anti-PD-1 antibody) as adjuvant therapy in patients with resected MM, and reported as superior to RFS (median RFS: 28.2 vs 12.0 months, $p=0.04$), DMFS (median DMFS: 42.0 vs 19.0 months, $p=0.02$), and OS (median OS: 93.4 vs 39.3 months, $p=0.03$) in the chemotherapy group (3). In this study, the salvage group tended to have a better OS than the adjuvant group, possibly because approximately half of the patients in the salvage group received cytotoxic chemotherapy as adjuvant therapy. Another possible reason is that the salvage group received a higher dose of PBT than the adjuvant group. In MMHN, Mizoguchi et al. compared the adjuvant and salvage ICI groups after carbon ion radiotherapy (CIRT) and reported no significant difference in OS ($p=0.122$) (4). However, for DMFS and PFS after CIRT, they reported that the adjuvant ICI group had significantly better DMFS ($p=0.008$) and PFS ($p=0.004$) than the group that did not receive adjuvant ICI therapy. Based on the findings of previous studies and the present analysis, it remains unclear whether adjuvant ICI therapy in MMHN improves prognosis after surgery and radiation therapy, as observed in CM.

This study has a few limitations. It was a retrospective cohort study, and selection bias may have been present in the 2 groups. Additionally, the small sample size may have limited the statistical power to detect differences. In conclusion, adjuvant ICI may not improve prognosis in patients with MMHN undergoing PBT, as observed in cutaneous malignant melanoma. Further studies are required to determine the optimal combination of systemic therapy, including chemotherapy, with PBT.

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Data availability statement: The data that support the findings of this study are available from the corresponding author [SY], upon reasonable request.

Ethics declarations: The study was reviewed and approved by the Ethics Committee of Shizuoka Cancer Center (2025/04/08); approval # 2025-7.

The authors have no conflicts of interest to declare.

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