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ORIGINAL RESEARCH

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The efficacy of PD-1 inhibitors in patients with salivary gland carcinoma: A retrospective observational study

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Abstract

Objective: Immune checkpoint inhibitors (ICIs) have been considered as novel therapeutic approaches for various cancers. ICIs were reportedly efficacious against rare cancers, including salivary gland carcinoma (SGC). We aimed to analyze the efficacy and safety of ICIs in patients with SGC.

Methods: We retrospectively analyzed the oncologic outcomes and immune-related adverse events (irAEs) in patients with SGC treated with at least one cycle of nivolumab or pembrolizumab.

Results: Among 12 patients, there were two with a complete response (CR), two with a partial response, five with stable diseases, and three with progressive diseases. The overall response rate was 33.3%. A CR was achieved in patients with poorly differentiated carcinoma (carcinoma ex pleomorphic adenoma) and salivary duct carcinoma. The progression-free survival ranged between 1 and 18 months (median, 4 months), while the overall survival ranged between 2 and 25 months (median, 13.5 months). An irAE was observed in only one patient who developed grade 3 erythema multiforme, and this patient's condition improved with withdrawal of pembrolizumab alone.

Conclusion: Programmed death-1 blockade was an effective therapy for patients with SGC, including aggressive histologic types.

KEYWORDS
nivolumab, PD-1 inhibitor, pembrolizumab, salivary gland carcinoma

1 | INTRODUCTION

Malignancies progress through immune evasion, which is mediated by the negative immune checkpoint, programmed death-1 (PD-1), and the programmed death ligand-1 (PD-L1) pathway.[1] Nivolumab and pembrolizumab, immune checkpoint inhibitors (ICI) targeting PD-1, are associated with prolonged overall survival (OS) in patients with various tumors.[1] The global phase III studies (Check Mate-141 and KEYNOTE-048) documented the effectiveness of PD-1 antibodies in patients with head and neck squamous cell carcinoma (SCC).[2,3] Both

TABLE 1 Patients characteristics and treatment outcomes

No.	Sex	Age	Primary site	At initial treatment				Histotype	Previous treatment	PD-L1 (CPS)	Type of the PD-1 inhibitor	Duration of treatment (mo)	Treatment status	BOR	PFS (mo)	OS (mo)	Outcome
				T	N	M	Stage										
1	M	68	Submandibular gland	3	2	1	IV	SDC	CTX	NA	Nivolumab	1	Discontinued (PD)	SD	1	2	DOD
2	M	75	Parotid gland	4	2	1	IV	MEC	CRT → CTX	NA	Nivolumab	4	Discontinued (PD)	SD	4	14	DOD
3	M	50	Parotid gland	4	0	0	IV	ACC	SR → RT → CTX	10%	Nivolumab	16	Discontinued (PD)	SD	16	17	DOD
4	M	72	Submandibular gland	1	1	0	III	SDC	SR → RT → CTX	5%	Nivolumab	6.5	Discontinued (PD)	PD	3	25	DOD
5	M	63	Parotid gland	4	0	1	IV	SCC	RT	NA	Pembrolizumab	18	Ongoing	PR	18	15	AWD
6	M	84	Parotid gland	4	0	0	IV	SCC	CRT → CTX	20%	Nivolumab	10.5	Discontinued (PD)	SD	7	15	DOD
7	F	77	Parotid gland	4	2	0	IV	carcinoma ex PA (SDC)	SR → CRT	100%	Nivolumab	4.5	Discontinued (PD)	PD	2	13	DOD
8	M	65	Parotid gland	4	2	1	IV	SDC	CTX	80%	Nivolumab	2	Discontinued (PD)	PD	2	5	DOD
9	M	60	Parotid gland	4	3	0	IV	carcinoma ex PA (PDC)	CRT → CTX	100%	Nivolumab	8.5	Ongoing	CR	8	8	NED
10	M	73	Submandibular gland	3	0	1	IV	SDC	CTX	10–19%	Pembrolizumab	16	Ongoing	CR	16	16	NED
11	M	65	Parotid gland	2	2	1	IV	SDC	CTX	10%	Pembrolizumab	2	Discontinued (irAE)	SD	4	5	AWD
12	M	74	Parotid gland	4	0	0	IV	carcinoma ex PA (MEC)	PBT	>20%	Pembrolizumab	3	Ongoing	PR	3	3	AWD

Abbreviations: ACC, adenoid cystic carcinoma; AWD, alive with disease; BOR, best objective response; CPS, combined positive score; CRT, chemoradiationtherapy; CTX, chemotherapy; DOD, died of disease; irAE, immune-related adverse event; MEC, mucoepidermoid carcinoma; mo, months; NA, not available; NED, no evidence of disease; OS, overall survival; PA, pleomorphic adenoma; PBT, proton-beam therapy; PD, progressive diseases; PDC, poorly-differentiated carcinoma; PD-L1, programed death ligand-1; PD-1, programmed death-1; PFS, progression free survival; RT, radiation therapy; SDC, salivary duct carcinoma; SR, surgical resection.

studies have demonstrated the survival benefits and safety profile in patients with recurrent or distant metastatic head and neck SCC. Although PD-1 was reportedly a poor prognostic marker for salivary gland carcinoma (SGC),[4] the efficacy of PD-1 inhibitors in patients with non-SCC head and neck carcinoma, including SGC, has not been fully elucidated. This study aimed to evaluate the efficacy and safety of PD-1 inhibitors in patients with SGC.

2 | MATERIALS AND METHODS

The medical records of patients with SGC treated with at least one cycle of nivolumab or pembrolizumab in the Department of Otorhinolaryngology Head and Neck Surgery of Kitami Red Cross Hospital or Asahikawa Medical University were retrospectively analyzed from September 2019 to November 2021. Because Pembrolizumab was approved in late 2019, we administered Nivolumab during September 2019–February 2020, and Pembrolizumab during March 2020–November 2021.

The progression and response, in terms of the best objective response, objective response rate (ORR), progression-free survival (PFS), and OS, were assessed according to the Response Evaluation Criteria in Solid Tumors 1.1 criteria.

Immune-related adverse events (irAEs) were analyzed according to the Common Terminology Criteria for Adverse Events version 5.0. The expression of PD-L1 in tumor cells and immune cells was assessed using the combined positive score (CPS) via tumor specimen sampling. CPS was defined as the total number of PD-1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells and multiplied by 100. This study followed the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. The study design was approved by the Ethics Review Board of the Kitami Red Cross Hospital and Asahikawa Medical University (#16217).

3 | RESULTS

The patient characteristics and oncologic outcomes of patients with SGC patients treated with PD-1 inhibitors are shown in Table 1. A total of 12 patients with SGC received PD-1 inhibitor treatment. The median age was 70 years (range, 50–84 years). There were 11 male patients and 1 female patient. Eleven patients were stage IV and another patient was stage III. Salivary duct carcinoma (SDC) was the most common histological type. There were five patients with SDC, three with carcinoma ex pleomorphic adenoma (PA), one with mucoepidermoid carcinoma patient (MEC), and one with adenoid cystic carcinoma (ACC). The histological types of the malignant component of carcinoma ex PA were poorly differentiated carcinoma (PDC), MEC, and SCC. Because the tumor was only located in parotid gland but not in skin, the origin of SCC was considered as parotid gland in two SCC cases. Although we considered surgical resection as a first-line treatment, the patients with distant metastasis or carotid invasion were initially treated with nonsurgical methods. The 10 of the 12 patients received at least one cycle of platinum-based chemotherapy. Of the other two patients, one received radiotherapy alone and the other received proton-beam therapy alone before PD-1 inhibitor treatment.

Eight patients were treated with nivolumab, while four were treated with pembrolizumab. All patients, who had been treated with nivolumab or pembrolizumab, received a PD-1 inhibitor every

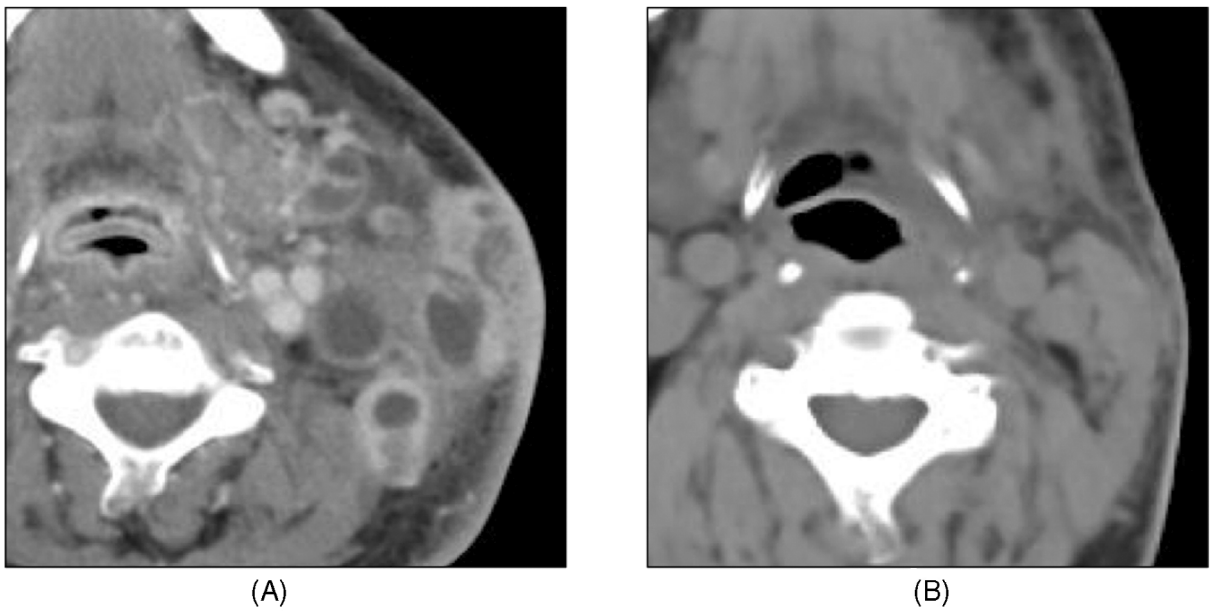

FIGURE 1 Computed tomography (CT) showing tumor disappearance of a left parotid mass and left neck metastasis in a patient with poorly differentiated carcinoma ex pleomorphic adenoma (case 9: A, B). (A) Enhanced CT of a left parotid mass and left neck metastasis before starting nivolumab. (B) Plain CT of the same lesion after administrating 11 cycles of nivolumab.

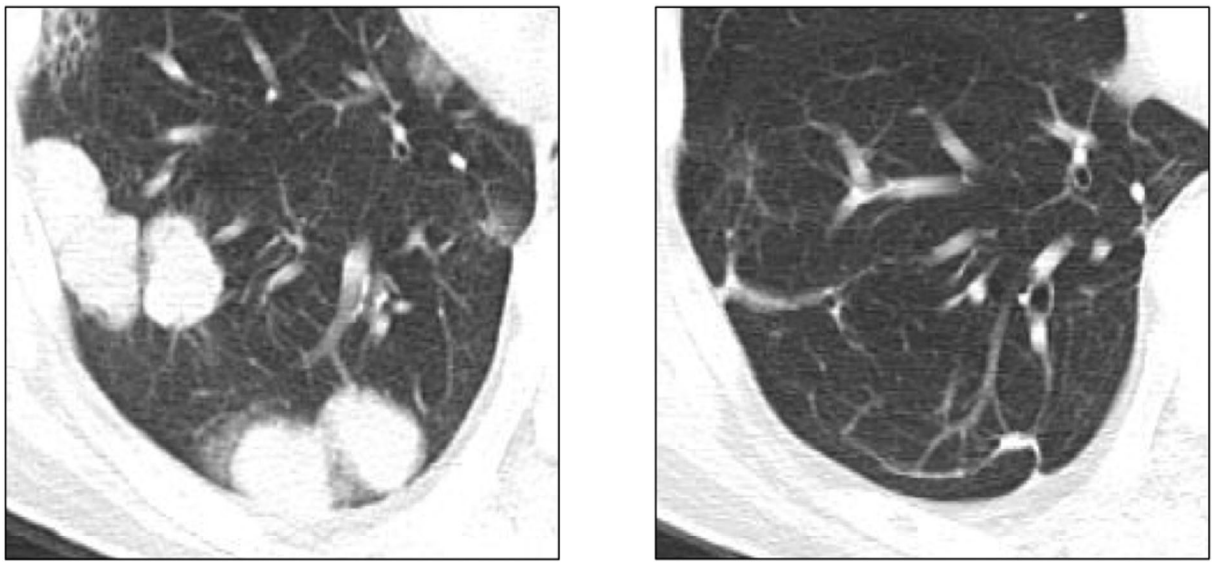

FIGURE 2 Computed tomography (CT) showing tumor disappearance of a right lung metastasis in a patient with salivary duct carcinoma (case 10: A, B). (A) Plain CT of a right lung metastasis before starting pembrolizumab. (B) Plain CT of the same lesion after administrating 17 cycles of pembrolizumab

2 weeks at a dose of 240 mg or every 3 weeks at a dose of 200 mg. The total number of nivolumab and pembrolizumab treatments ranged between 2 and 32 (median: 11 times) and between 3 and 24 times (median: 11.5 times), respectively. The PD-1 inhibitors were administered for a median period of 5.5 months (1–18 months). Among the 12 patients, there were two patients with a complete response (CR) (Figures 1, 2), two patients with a partial response (PR), five patients with stable disease (SD), and three patients with progressive disease (PD). The ORR was 33.3%. The histologic types of the patients who achieved CR were carcinoma ex PA (PDC) and SDC, and those of the patients who achieved PR were SCC and carcinoma ex PA (MEC). The PFS ranged between 1 and 18 months (median, 4 months), while the OS ranged between 2 and 25 months (median, 13.5 months). Eight patients discontinued PD-1 inhibitors because of disease progression or irAE (Table 1). The expression of PD-L1 in the tumor specimens was assessed in nine patients. PD-L1 staining was unavailable in the three patients whose diagnosis was made by a small biopsy sample or cytology. The CPS varied between 10% and 100% and 5% and 100% in responders and nonresponders, respectively. An irAE was observed in only one patient with SDC (No. 11) who developed grade 3 erythema multiforme. The patient's condition improved after withdrawal of pembrolizumab.

4 | DISCUSSION

SGC is a rare malignancy, accounting for less than 3% of all head and neck carcinomas. It consists of a broad spectrum of histologic types. The principal treatment for SGC is tumor resection. As patients with SGC are often diagnosed at advanced stages, with surrounding tissue infiltration, a complete tumor resection is not always feasible. SGC recurrence is still possible even after complete tumor resection.[5,6] Thus, nonsurgical treatment is warranted. Owing to the various histologic types of SGC, a standard chemotherapy regimen has not been established.[5,6] Although clinical trials for molecule-targeted therapies, such as HER2 inhibitors, have been attempted, these therapies were only used for specific tumor types, including SGC.[6]

The present study documented the effectiveness and tolerability of PD-1 inhibitors in patients with SGC. The ORR was 33.3%, and only one patient showed an irAE, which was improved by withdrawal of pembrolizumab alone. The efficacy and safety of PD-1 inhibitor monotherapy for patients with SGC, based on previous studies, is summarized in Table 2.[7–9] Among the 69 patients reported in the literature, including this study, there were three patients with CR, 7 with PR, 32 with SD, and 27 with PD. Thirty-six patients received nivolumab, while 33 patients received pembrolizumab. The ORR was 14.5%. The median PFS and OS were 2.1–4 months and 7.7–13.5 months, respectively. Two out of the three studies demonstrated the efficacy of PD-1 inhibitors for SGC. Grade 3 or 4 irAE events were observed in 5/47 cases (10.6%). The frequency of irAE in patients with SGC was comparable to other types of carcinomas.[10] The results of the present study showed the highest ORR among these studies. These differences were likely due to the diverse patient characteristics. A predictive biomarker for PD-1 inhibitor treatment should be established to determine the appropriate patients with SGC.

Located in tumor and immune cells, PD-L1 promotes immunosuppression along with PD-1, expressed in activated T cells. PD-L1 expression in tumor and immune cells was reportedly predictive of the anti-tumor effect and treatment outcomes of PD-1 inhibitors. CPS was reportedly more effective than other PD-L1 scoring systems in

TABLE 2 The literature summary of PD-1 inhibitor monotherapy in patients with SGC

Study	Number of patients	Types of PD-1 inhibitors	BOR				ORR	Median PFS (mo)	Median OS (mo)	Grade 3 or 4 irAE (%)					Discontinued treatment for irAE
			CR	PR	SD	PD				Lung	Skin	Liver	Blood	All	
Hanai et al.	22	Nivolumab	1	2	9	10	13.6%	2.1	7.7	NA	NA	NA	NA	NA	NA
Cohen et al.	29	Pembrolizumab	0	3	15	11	10.3%	4	13	1 (3.4)	1 (3.4)	1 (3.4)	1 (3.4)	4 (13.8)	3 (10.3)
Kokkali et al.	6	Nivolumab	0	0	3	3	0%	2.75	11.5	–	–	–	–	–	0
Our study	12	Nivolumab/ Pembrolizumab	2	2	5	3	33.3%	4	13.5	–	1 (8.3)	–	–	1 (8.3)	1 (8.3)

Abbreviations: BOR, best objective response; irAE, immune-related adverse event; NA, not available; ORR, objective response rate; OS, overall survival; mo, months; PD-1, programmed death-1; PFS, progression free survival; SGC, salivary gland carcinoma.

correlating the clinical response to PD-1 inhibitors in head and neck SCC.[11] In our study, the responsive SGC patients had high-CPS scores (100%, 10%–19%, and >20%). However, some patients with high-CPS scores did not achieve clinical responses. Because the biopsy sample might not be a representative to examine PD-L1 of the whole tumor[12] and the expression of PD-L1 is inconsistent, it would be difficult to consider PD-L1 expression in the biopsy sample as a biomarker to select ICI responders.

As the clinical course varies depending on the histologic type of SGC, the efficacy of PD-1 inhibitors should be analyzed for each histologic type.[5] In this study, most patients, including responders, exhibited the aggressive histologic types. Patients with carcinoma ex PA, SCC, and SDC, the histologic types categorized as aggressive types,[5] responded to PD-1 blockade. The aggressive SGC types reportedly had high PD-L1 expression and tumor mutational burden, both of which are predictive factors of PD-1 inhibitors.[11,13,14] Thus, aggressive SGC types are likely good targets for PD-1 inhibitors. In this study, CR patients have been continuing PD-1 inhibitors. The results from the ongoing clinical trials to evaluate the prognosis after withdrawing PD-1 inhibitors[15] would contribute establishing the criteria to discontinue PD-1inhibitors in CR patients.

This study had several limitations. First, this was an observational retrospective study without a control group, and the observation period was short. In other types of carcinomas, some patients had a favorable long-term survival even when the tumor progressed with PD-1 inhibitors.[7,16] Thus, a prospective controlled trial evaluating the long-term survival effect of PD-1 inhibitors on patients with SGC should be conducted. Second, a statistical analysis regarding the predictive factors of PD-1 inhibitors was not conducted, and CPS was not analyzed in all patients. Although aggressive histologic types were implied as positive predictive factors in this study, further examinations are necessary to investigate the predictive biomarkers of PD-1 inhibitors in SGC. Because the rarity of disease, it was difficult to recruit the patients with same type of tumor in this study. Further studies are necessary to conclude whether PD-1 blockade is effective in each type of SGC.

5 | CONCLUSIONS

This study documented the efficacy and safety of PD-1 inhibitors for SGC. A favorable ORR of 33.3% was achieved. Despite the small sample size, aggressive tumor types were identified as predictive factors of PD-L1 inhibitors. Further examination regarding the long-term efficacy and predictive factors of PD-1 inhibitors in patients with SGC is required.

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CONFLICT OF INTEREST

None declared.

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