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# Complete Response to Nivolumab of Resected Adenocarcinoma NOS With Parotid Gland Origin and Lung Metastasis

YUI NEGISHI[1], ISAKU OKAMOTO[1], YURI UEDA[1], HIROKI SATO[1], MAKI TANIGAWA[2], TOSHITAKA NAGAO[2] and KIYOAKI TSUKAHARA[1]

[1]*Department of Otorhinolaryngology, Head and Neck Surgery, Tokyo Medical University, Tokyo, Japan;*
[2]*Department of Anatomic Pathology, Tokyo Medical University, Tokyo, Japan*

**Abstract.** *Background/Aim: Salivary gland adenocarcinoma not otherwise specified (NOS) is classified under the 2017 WHO Classification of Head and Neck Tumors as a malignant neoplasm without the histological features characteristic of other cancer types. Japan's national health insurance program began covering nivolumab in March 2017 for the treatment of patients with recurrent or metastatic head and neck cancer, including salivary gland carcinoma, previously treated with platinum agents. Existing literature does not include cases of patients with salivary gland carcinoma, adenocarcinoma NOS or otherwise, who have achieved complete response to nivolumab. Case Report: Our patient was a 32-year-old woman. Following diagnosis of adenocarcinoma of a right accessory parotid gland, she underwent reconstructive surgery of the parotid gland followed by postoperative adjuvant therapy with radiotherapy and cisplatin. Multiple lung metastases were found 14 months thereafter. Given a history of cisplatin administration, she was treated with nivolumab. Computed tomography (CT) showed partial response after 5 months and complete response after 9 months of nivolumab treatment. Based on CT findings, the lung metastases remained absent 39 months after nivolumab treatment was halted due to the patient's plans for pregnancy. Conclusion: Nivolumab may be an effective option for treating high-grade salivary gland carcinomas that recur or metastasize.*

*Correspondence to:* Isaku Okamoto, MD, Ph.D., Department of Otorhinolaryngology, Head and Neck Surgery, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan. Tel: +81 333426111, Fax: +81 333469275, e-mail: isaku@tokyo-med.ac.jp

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Salivary gland adenocarcinoma not otherwise specified (NOS) is classified under the 2017 WHO Classification of Head and Neck Tumors as a malignant neoplasm without the histological features characteristic of other cancer types (1). Surgery is the standard treatment for salivary gland carcinomas of all histopathological types. High-grade salivary gland carcinoma is often treated with postoperative radiotherapy. The effect of adding chemotherapy to radiotherapy remains largely undocumented. No consensus has been reached regarding a standard regimen for salivary gland carcinoma that has distant metastases or is unresectable. In March 2017, the national health insurance program in Japan began covering nivolumab therapy for the treatment of patients with recurrent or metastatic head and neck cancer previously treated using platinum agents (2). The national insurance system in Japan, unlike that in most other countries, covers nivolumab for in the treatment of salivary gland carcinoma patients previously treated with a platinum agent. Current literature does not appear to mention any cases of patients with salivary gland carcinoma who have responded to nivolumab. Herein, we discuss the case of complete response to nivolumab in a patient who received the drug following the appearance of multiple lung metastases of curatively resected adenocarcinoma NOS, originating in an accessory parotid gland.

## Case Report

The patient was a 32-year-old woman who complained of a swollen sensation in the cheekbones. She had no medical history but had an allergy to sulfur. She had no history of smoking or drinking. On presentation, the patient showed palpable swelling of the right cheek. Facial nerve paralysis was absent. Computed tomography (CT) revealed an irregular mass measuring 34×14 mm superior to the masseter muscle. Based on findings from CT and fine-needle biopsy of the affected area, high-grade carcinoma was diagnosed. Positron emission tomography (PET)/CT and other imaging modalities resulted in a diagnosis of a T3N0M0 stage III accessory parotid gland adenocarcinoma.

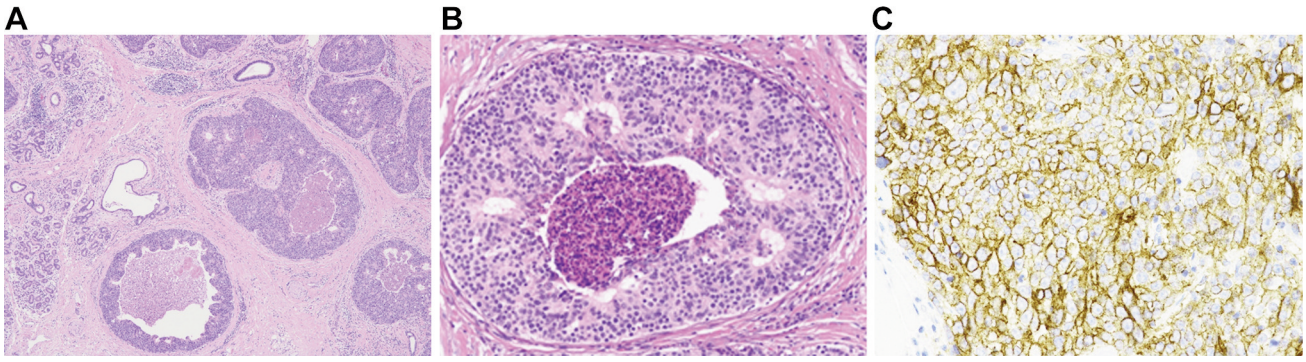


Figure 1. *Pathologic evaluation showed, within the tumor, alveolar sites of varying sizes formed by atypical cells with a high nuclear-to-cytoplasmic ratio. A) Hematoxylin and eosin stain (×40). B) Hematoxylin and eosin stain (×20). C) PD-L1 (×40).*

We performed total resection of the right accessory parotid gland, level I-IV dissection of the right neck, reconstruction with an anterolateral thigh flap, static and dynamic facial nerve reconstruction, and tracheostomy. The patient lost 199 ml of blood during the 13 h 49 min operation. She recovered well and was discharged after 14 days. Pathologic evaluation (Figure 1A and B; hematoxylin and eosin staining) showed, within the tumor, alveolar sites of varying sizes formed by atypical cells with a high nuclear-to-cytoplasmic ratio. These sites showed infiltrating growth and substantial central necrosis. The atypical cells showed swollen, ovate to irregularly shaped nuclei that were darkly stained or had distinct micronuclei, and rosette-like to glandular structures were prominent. Atypical cells with a very high nuclear-to-cytoplasmic ratio and atypical cells with relatively abundant eosinophilic (granular) cytoplasm were interspersed. Extensive venous invasion (v3) and moderate perineural invasion (pn2) were noted. The surgical margins, including the facial nerve margins, were positive. Immunohistochemical findings were as follows: cytokeratin AE1/AE3 (+), AR (–), GCDFP-15 (–), HER2 (1+), CD56 (partially positive), chromogranin A (partially positive), synaptophysin (partially positive), and Ki-67 labeling index (50%). Programmed cell death ligand 1 (PD-L1) expression was 50% (Figure 1C). Dako 28-8 antibody (Dako, Carpinteria, CA, USA) as measured in Checkmate-141 was used for immunohistochemical assay. Adenocarcinoma NOS was diagnosed based on these findings. Although metastases were seen in two lymph nodes associated with the parotid gland, no extranodal involvement was evident. Concurrent chemoradiation therapy with cisplatin (CDDP) was administered because the surgical margins were positive and comprised three courses of CDDP administered at 80 mg/m$^2$. The total radiation dose was 60 Gy/30 Fr. Cervicothoracic CT performed 14 months after concurrent chemoradiation therapy revealed three lung nodules in the right lung field (Figure 2). Although no nodule measured

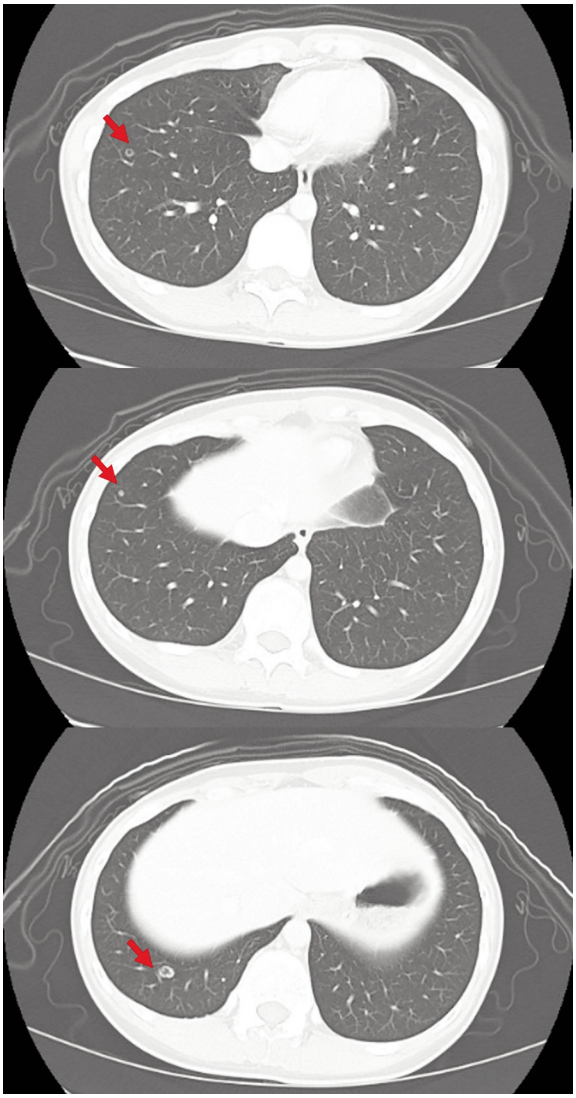

Figure 2. *Computed tomography images taken at the time lung metastases appeared. Nodular, ring-shaped areas are seen at three locations in the right lung (arrows indicate lung metastases).*

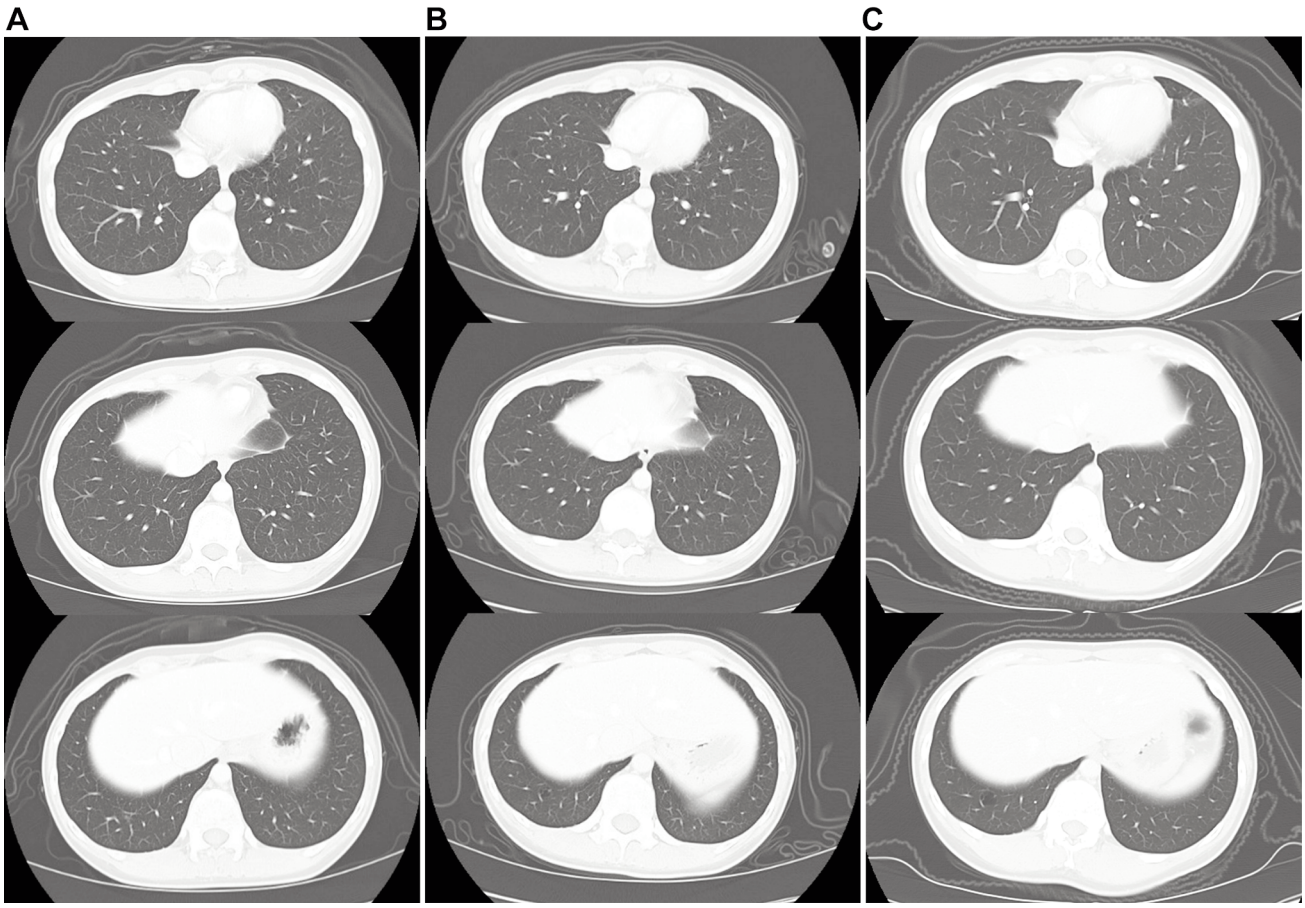


Figure 3. *Computed tomography images after starting nivolumab treatment. A) Image taken at 5 months. B) Image taken at 9 months. C) Image taken at 39 months (13 months after stopping nivolumab treatment).*

>10 mm, a multidisciplinary cancer board that included a diagnostic radiologist concluded that the findings revealed multiple lung metastases. The board concluded that the patient fulfilled the indication criteria for nivolumab because she had head and neck cancer previously treated using CDDP and 50% of the removed specimen stained positively for anti-PD-L1 antibody.

The three lung metastases imaged using CT 5 months after starting nivolumab treatment (Figure 3A) had shrunk; constituting a partial response (PR). Based on CT findings, the lung metastases were absent 9 months after the start of nivolumab treatment (Figure 3B). As no new lesions were evident, the patient was assessed as having achieved complete response. She experienced no immune-related adverse events. Based on CT findings, the lung metastases remained absent 39 months after stopping nivolumab treatment because of the patient's plans for pregnancy (Figure 3C). Furthermore, 13 months after discontinuation of nivolumab treatment, the patient had no recurrence or metastasis, and her quality of life remained good.

## Discussion

In the CheckMate 141 trial, nivolumab prolonged overall survival in oropharyngeal, hypopharyngeal, and laryngeal cancers (2). The relevant National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines classify nivolumab as a category 1 treatment for recurrent or metastatic head and neck cancers (3), the same as the EXTREME regimen (4). Japanese national health insurance covers nivolumab for recurrent or metastatic head and neck cancer previously treated with CDDP, without restrictions on the primary site or histopathological classification. This is a very rare report of a patient who had a long-lasting complete response to nivolumab for multiple lung metastases to adenocarcinoma of the accessory parotid gland. High-grade adenocarcinoma NOS carries a 5-year survival rate of <50% (1). High-grade salivary gland carcinoma is often treated with postoperative radiotherapy. The benefit chemotherapy adds to radiotherapy is unknown. This combination is classified as category 2B in the NCCN guidelines (3). Our

department administers concurrent chemoradiation therapy with CDDP for salivary gland carcinoma, as with other head and neck cancers, if the condition of the patient allows it. Carboplatin and paclitaxel (5); paclitaxel monotherapy; (6) and cisplatin, doxorubicin, and cyclophosphamide (7) have been used to treat salivary gland carcinoma that has distant metastases or is unresectable, but no standard regimen has been established. We selected nivolumab for the present patient because no evidence-supported option was available, anti-PD-L1 antibody staining amounted to 50%, and health insurance covered nivolumab.

CT showed partial response after 5 months and complete response from 9 to 39 months. Once postoperative recurrence or distant metastasis has occurred, high-grade salivary gland carcinoma is highly refractory to treatment and has few treatment options. We believe that nivolumab should be started while distant metastases are still small, as in our patient. Theoretically, nivolumab should be effective against high-grade salivary gland carcinoma carrying many mutations. We hope that this report benefits the treatment of salivary gland carcinoma.

## Conclusion

This case report describes a rare patient with multiple lung metastases from adenocarcinoma of the accessory parotid gland who had a long-lasting complete response to nivolumab. Nivolumab may be an effective treatment option for high-grade salivary gland cancer.

## Conflicts of Interest

All Authors have no conflicts of interest, potential conflicts, or financial relationships to disclose in relation to this study.

## Authors' Contributions

IO developed the case report. YN wrote the main article text and prepared the figures. IO, YN, YU, HS and KT oversaw the treatment of this patient. IO, YN, YU, HS, MT, TN, and KT were involved in the data collection. All Authors discussed the results of the case report, made comments on the article, and gave final approval of the version to be published.

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## References

1 El-Naggar AK, Chan JKC, Grandis JR, Takata T and Slootweg PJ: WHO classification of head and neck tumours. 4th ed. International Agency for Research on Cancer, pp. 347, 2017.

2 Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Iglesias Docampo LC, Haddad R, Rordorf T, Kiyota N, Tahara M, Monga M, Lynch M, Geese WJ, Kopit J, Shaw JW and Gillison ML: Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med *375(19)*: 1856-1867, 2016. PMID: 27718784. DOI: 10.1056/NEJMoa1602252

3 National Comprehensive Cancer Network (NCCN): Clinical Practice Guidelines in Oncology, Head and Neck Cancers (Version 3.2021). Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck_blocks.pdf [Last accessed on July 7, 2022]

4 Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, Erfan J, Zabolotnyy D, Kienzer HR, Cupissol D, Peyrade F, Benasso M, Vynnychenko I, De Raucourt D, Bokemeyer C, Schueler A, Amellal N and Hitt R: Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med *359(11)*: 1116-1127, 2008. PMID: 18784101. DOI: 10.1056/NEJMoa0802656

5 Nakano K, Sato Y, Sasaki T, Shimbashi W, Fukushima H, Yonekawa H, Mitani H, Kawabata K and Takahashi S: Combination chemotherapy of carboplatin and paclitaxel for advanced/metastatic salivary gland carcinoma patients: differences in responses by different pathological diagnoses. Acta Otolaryngol *136(9)*: 948-951, 2016. PMID: 27094013. DOI: 10.3109/00016489.2016.1170876

6 Tahara M, Minami H, Hasegawa Y, Tomita K, Watanabe A, Nibu K, Fujii M, Onozawa Y, Kurono Y, Sagae D, Seriu T and Tsukuda M: Weekly paclitaxel in patients with recurrent or metastatic head and neck cancer. Cancer Chemother Pharmacol *68(3)*: 769-776, 2011. PMID: 21181475. DOI: 10.1007/s00280-010-1550-3

7 Licitra L, Cavina R, Grandi C, Palma SD, Guzzo M, Demicheli R and Molinari R: Cisplatin, doxorubicin and cyclophosphamide in advanced salivary gland carcinoma. A phase II trial of 22 patients. Ann Oncol *7(6)*: 640-642, 1996. PMID: 8879381. DOI: 10.1093/oxfordjournals.annonc.a010684

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