

## CASE REPORT

# Is chemoimmunotherapy a game changer in the treatment of locally advanced head and neck squamous cell carcinoma?

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**Abstract**

Pembrolizumab and chemotherapy (chemoimmunotherapy) were administered to 2 head and neck squamous cell carcinoma (HNSCC) patients with extremely advanced local tumors and distant metastases with palliative intent. However, they demonstrated strikingly good responses and achieved remission. Expanded application of induction chemoimmunotherapy may be useful for locally advanced HNSCC.

**KEYWORDS**

advanced head and neck cancer, chemoimmunotherapy, chemotherapy, pembrolizumab

## 1 | INTRODUCTION

The introduction of immune checkpoint inhibitor (ICI) opened a new era in the treatment of patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN).<sup>1</sup> In the CheckMate 141 study that targeted platinum refractory patients, 16.9% of the selected patients survived for >2 years; this survival duration could not be achieved using conventional chemotherapeutic regimens.<sup>2</sup> Considering the favorable results of KEYNOTE 048, pembrolizumab alone and pembrolizumab with chemotherapy were approved in Japan in September, 2019 as the first-line regimen for R/M SCCHN.<sup>3</sup> Here, we describe our experiences in the management of two consecutive patients with locally advanced tumors and distant metastases who were treated with pembrolizumab and chemotherapy (chemoimmunotherapy). In both these cases, the tumors were extremely advanced; therefore, we chose this regimen with a palliative intent. However, they demonstrated good responses and achieved remission.

## 2 | CLINICAL CASE PRESENTATION

### 2.1 | Case 1

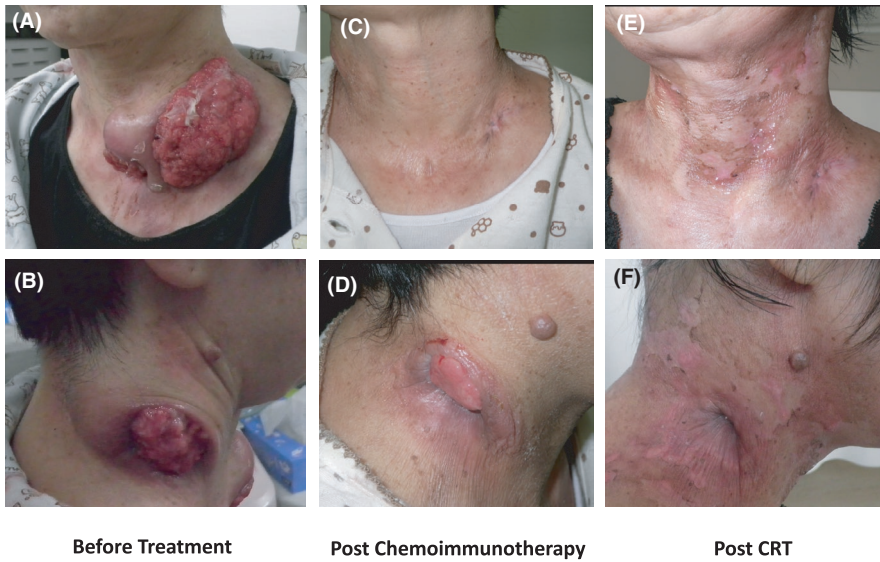
A 73-year-old woman was referred to our hospital with dysphagia and large masses on the both sides of her neck (Figure 1A, B). The extent of disease was examined using endoscope, computed tomography (CT), magnetic resonance imaging, and fluorodeoxyglucose-positron emission tomography. We detected a hypopharyngeal tumor located in the right piriform sinus extending to the cervical esophagus. Multiple bilateral lymph node (LN) metastases with extranodal extension and mediastinal LN metastases below level VII were observed. The biopsy sample of the hypopharyngeal tumor was pathologically proven to be squamous cell carcinoma (SCC). Thus, T3N3bM1 hypopharyngeal SCC was diagnosed as per the American Joint Committee on Cancer's Cancer Staging Manual, 8<sup>th</sup> edition. The cervical lymph nodes

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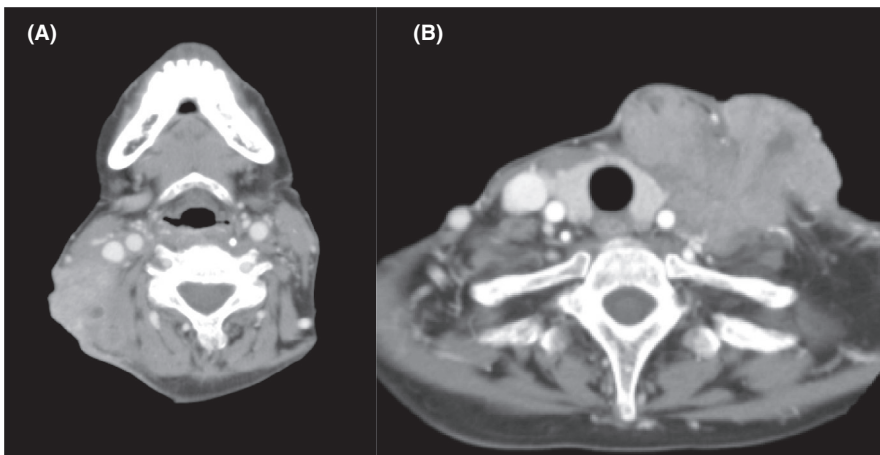
invaded and passed through the skin, particularly, the left subclavian lymph nodes were entangled and formed a huge mass blooming outwardly (Figure 1A, B). The left common carotid artery and the internal jugular

vein were encased by the lymph nodes (Figure 2A, B). We judged that curative surgical removal of the tumor was not feasible. Her tumor demonstrated 5% of combined positive score (CPS) for programmed cell death

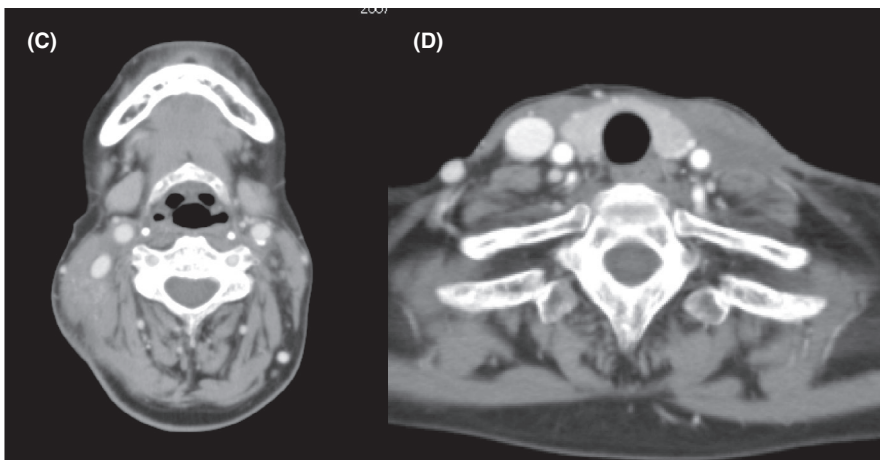


**FIGURE 1** Photographs of the neck of Case 1. Before treatment (A and B), after 3 cycles of chemoimmunotherapy (C and D), and consequent concurrent chemoradiotherapy (CRT) (E and F)

### Before Treatment



### Post Chemoimmunotherapy



**FIGURE 2** Contrast-enhanced computed tomography imaging in Case 1. Before treatment (A and B), after 3 cycles of chemoimmunotherapy (C and D)

ligand (PD-L)1 immunostaining (22C3 pharmDx). The multidisciplinary cancer board recommended the administration of pembrolizumab (200 mg/body) plus chemotherapy (5-FU 800 mg/m<sup>2</sup> per day for 4 days and cis-platinum 80 mg/m<sup>2</sup>), aiming to provide a palliative effect. With three cycles of chemoimmunotherapy, the tumors showed remarkable reduction in size (Figure 1C, D). The primary tumor demonstrated complete response (CR), and the huge left LN turned into a scar without enhancement on CT imaging (Figure 2C, D). However, the right LN with skin ulcer continued to give partial response (PR) (Figure 2C). The mediastinum LN also showed CR; therefore, 70 Gy of chemoradiotherapy (80 mg/m<sup>2</sup> of cis-platinum × 2) was given with a curative intent as the second-line treatment. The right LN responded well to chemoradiotherapy and caused scar formation (Figure 1E, F). After treatment, she has been alive with no sign of tumor regression for 6 months.

## 2.2 | Case 2

A 73-year-old man visited a local hospital with a right neck mass, severe dysphagia, and acute weight-loss of 14 kg in 2 months. A needle biopsy for the neck mass revealed

undifferentiated SCC; he was referred to our hospital. He consumed only liquid food; however, he developed aspiration pneumonia owing to the right vocal cord paralysis and severe stenosis of the esophagus. A CT demonstrated a >10-cm mass that replaced the right thyroid lobe and involved the right common carotid artery, internal jugular vein, and cervical and upper thoracic esophagus (Figure 3A-C). The membranous part of the trachea was invaded by the tumor (Figure 3B). Right accessory chain LNs swelling and mediastinal LNs metastasis below level VII were observed. Considering the pattern of the tumor extension and complete loss of thyroid tissue sign in the CT imagings, SCC of thyroid T4bN1M1 was diagnosed as per the American Joint Committee on Cancer's Cancer Staging Manual, 8<sup>th</sup> edition. As his tumor was unresectable, best supportive care or chemoimmunotherapy that is approved in Japan for treating thyroid SCC with distant metastasis was considered by the multidisciplinary cancer board. In this case, measurement of PD-L1CPS was not conducted because an adequate biopsy sample was not available. The patient chose to undergo chemoimmunotherapy; therefore, he was administered pembrolizumab (200 mg/body) plus 5-FU (800 mg/m<sup>2</sup> per day for 4 days), and cis-platinum (80 mg/m<sup>2</sup>), after his aspiration pneumonia subsided with antibiotic administration and nasogastric tube feeding. His tumors demonstrated

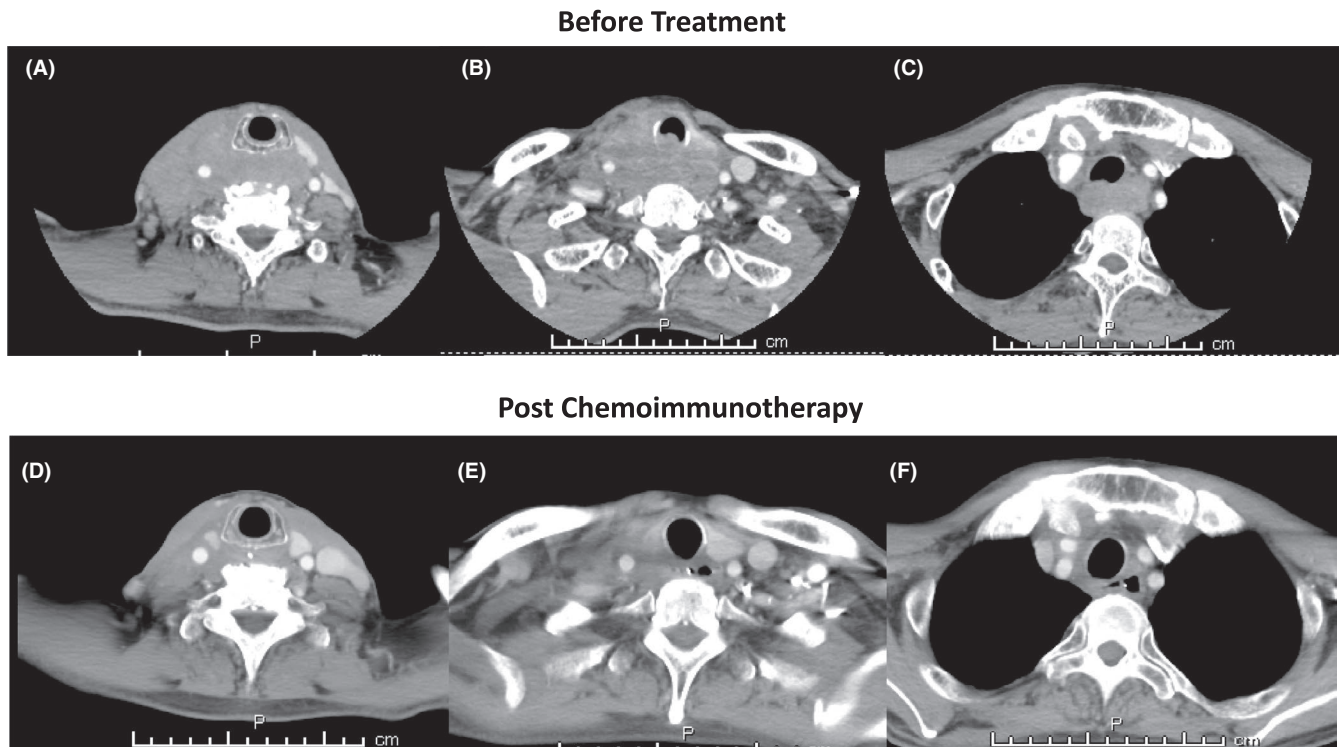


FIGURE 3 Contrast-enhanced computed tomography CT imaging in Case 2. Before treatment (A, B, and C) and after 3 cycles of chemoimmunotherapy (D, E, and F)

unexpectedly favorable responses. After two cycles of chemoimmunotherapy, he resumed normal food intake and after 3 cycles, and CR was achieved (Figure 3D-C). The patient is leading a normal, healthy life, 8 months after treatment.

### 3 | DISCUSSION

ICI demonstrates distinctive effects in the treatment of SCCHN. In our present study based on daily medical practice,<sup>4</sup> nivolumab administration resulted in significantly better 1-year overall survival (54.4%) than the CheckMate 141 (36%).<sup>2</sup> Thus, the real-world data were superior to those obtained from randomized control trials (RCT), which was an unseen phenomenon in the previous RCT that used chemo/radiotherapeutic regimen. Here, we demonstrated notable experiences of two patients with locally advanced SCCHN who were treated with chemoimmunotherapy. Their tumors were expected to be uncontrollable because empirically or statistically huge LNs invade the skin and thyroid SCCs are refractory to chemo/radiotherapeutic agents, and are associated with extremely poor prognosis.<sup>5</sup> However, with chemoimmunotherapy, we were able to achieve tumor remission and substantial improvement in the patient's quality of life. As shown in several reports including ours, salvage chemotherapy after ICI demonstrates unexpectedly drastic effects for selected cases.<sup>6,7</sup> Although the precise mechanism of this interaction is not known, it is estimated that preceding administration of ICI can activate the immune system and change the natural history of the disease and the microenvironment, rendering tumor cells more sensitive to chemotherapy.<sup>7</sup> However, it is elusive this scenario is applicable to the simultaneous administration of ICI and chemotherapy, because in the R/M setting of KEYNOTE048,<sup>3</sup> chemoimmunotherapy didn't achieve superior responses to Pembrolizumab alone. We speculate that synergistic tumor killing effect of ICI and chemotherapeutic agent may prone to occur in the treatment-naïve tumors as seen in this study. However, this possibility has to be confirmed in the future study.

Currently, the use of chemoimmunotherapy is confined to the R/M setting across the world. Whereas, our data indicate the usefulness of induction chemoimmunotherapy for patients with locally advanced SCCHN. This may lead to the improved survival and organ preservation, particularly laryngeal preservation in the T3 or T4 larynx and hypopharynx patients. Further prospective multi-institutional studies are warranted.

### 4 | CONCLUSION

We experienced drastic effects of chemoimmunotherapy for locally advanced SCCHN.

#### ACKNOWLEDGEMENTS

None.

#### CONFLICT OF INTEREST

We have nothing to disclose.

#### AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: Masuda M, Toh S Higaki Y; data collection: Nagata R, Rikimaru F, Hara H, Kuroki K; analysis and interpretation of results: Masuda M, Sato K; draft manuscript preparation: Masuda MY. All authors reviewed the results and approved the final version of the manuscript.

#### ETHICAL APPROVAL

This study was approved by IRB.

#### CONSENT

Written informed consent was obtained from the patients.

#### DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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