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Chemotherapy in Combination With Methionine Restriction Induced A Complete Response in a Patient With Recurrent Metastatic Tongue Squamous-Cell Carcinoma

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Abstract

Background/Aim: Recurrent head and neck squamous-cell carcinoma (HNSCC) is associated with poor prognosis and limited treatment options, particularly after failure of standard therapies including surgery, radiotherapy, chemotherapy, and immune checkpoint inhibitors. Methionine restriction has emerged as a novel clinical metabolic therapeutic strategy targeting the methionine addiction of cancer cells. The present patient report describes a case of recurrent tongue HNSCC that achieved complete remission with chemotherapy combined with methionine restriction.
Case Report: A 35-year-old man was diagnosed with HNSCC of the left lateral border of the tongue (cT2N2bM0, Stage IVA). The patient underwent curative-intent surgery consisting of partial glossectomy and neck dissection. Despite multimodal treatment, including induction chemotherapy, salvage surgery, postoperative chemoradiotherapy, and subsequent immune checkpoint inhibitor therapy, the tumor recurred in the left submandibular region. Following further progression, combination chemotherapy with paclitaxel and cetuximab was administered in combination with methionine restriction (MR), consisting of a low-methionine diet and oral recombinant methioninase (rMETase), rMETase was produced using recombinant *Escherichia coli* expressing the *methioninase* gene from *Pseudomonas putida* and purified by standard methods. Tumor metabolic activity was evaluated using [^{18}F]fluorodeoxyglucose positron-emission tomography (PET)/computed tomography (CT) performed according to standard clinical protocols. Rapid tumor regression was observed. Follow-up magnetic resonance imaging (MRI) and PET/CT demonstrated complete response, which was maintained after de-escalation to cetuximab combined with MR.
Conclusion: The present case demonstrates the potential clinical efficacy of combining chemotherapy with MR in the treatment of recurrent HNSCC after curative-intent surgery and failure of standard therapies, including immune

continued

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checkpoint inhibition. MR may represent a promising metabolic therapeutic approach for refractory HNSCC. Additional cases and prospective clinical trials are necessary.

Keywords: Squamous-cell carcinoma, tongue, recurrence, chemotherapy, combination, methionine restriction, oral methioninase, remission, Hoffman effect.

Introduction

Head and neck squamous-cell carcinoma (HNSCC) has a high incidence and high mortality (1). Major etiological factors include tobacco use, alcohol consumption, and infection with human papillomavirus, with considerable geographic variability in disease prevalence (2). While early-stage HNSCC often responds to therapy with surgery and/or radiotherapy, many patients are initially diagnosed with advanced disease (3, 4).

Advanced HNSCC is generally treated by surgery, radiotherapy, and systemic chemotherapy (5). Although these therapies may achieve disease control, they are frequently associated with substantial morbidity, including impairment of swallowing and speech, as well as cosmetic deformity, resulting in diminished quality of life (6-8). Despite improvements in therapeutic techniques, disease recurrence remains recalcitrant (9-11).

Even after curative-intent therapy, locoregional relapse or distant metastasis may occur (12, 13). Once recurrence develops, treatment options are limited by therapeutic resistance and reduced responsiveness to conventional agents (14). Salvage strategies, such as chemotherapy, immune checkpoint inhibition, and re-irradiation, yield durable remission in only a minority of patients (15, 16). Accordingly, there is a pressing need to explore alternative therapeutic approaches capable of overcoming resistance in recurrent HNSCC.

Methionine addiction is a cancer metabolic vulnerability in which cancer cells exhibit a strong dependence on exogenous methionine, and is a fundamental and general hallmark of malignancy, termed the Hoffman effect (17, 18). This vulnerability can be therapeutically targeted through methionine restriction (MR) using a low-methionine diet in combination with recombinant methioninase (rMETase). Preclinical investigations have demonstrated MR effects antitumor activity on a wide range of cancer types (18, 19). In addition, methionine restriction has been reported to enhance the antitumor efficacy of cytotoxic chemotherapy, demonstrating its potential as a combination strategy (20).

The development of an orally-available formulation of rMETase has further facilitated the feasibility of implementing methionine-restriction–based interventions in the outpatient setting (21, 22).

Previously a patient with primary squamous-cell carcinoma of the tongue was treated with methionine restriction and chemotherapy and had a complete response (4).

In the present study we describe a case of recurrent squamous-cell carcinoma of the tongue which was put into remission by a combination of chemotherapy and methionine restriction.

Materials and Methods

rMETase was produced by fermentation of recombinant *Escherichia coli* transformed with the *methioninase* gene derived from *Pseudomonas putida* and purified as described elsewhere (23).

Case Report

A 35-year-old man presented with a persistent oral ulcer–like lesion since July 2023 and was diagnosed with squamous-cell carcinoma of the left lateral tongue (cT2N2bM0, stage IVA) at the National Cancer Center Hospital, Tokyo, Japan, on September 8th, 2023. The patient underwent partial glossectomy and left-neck

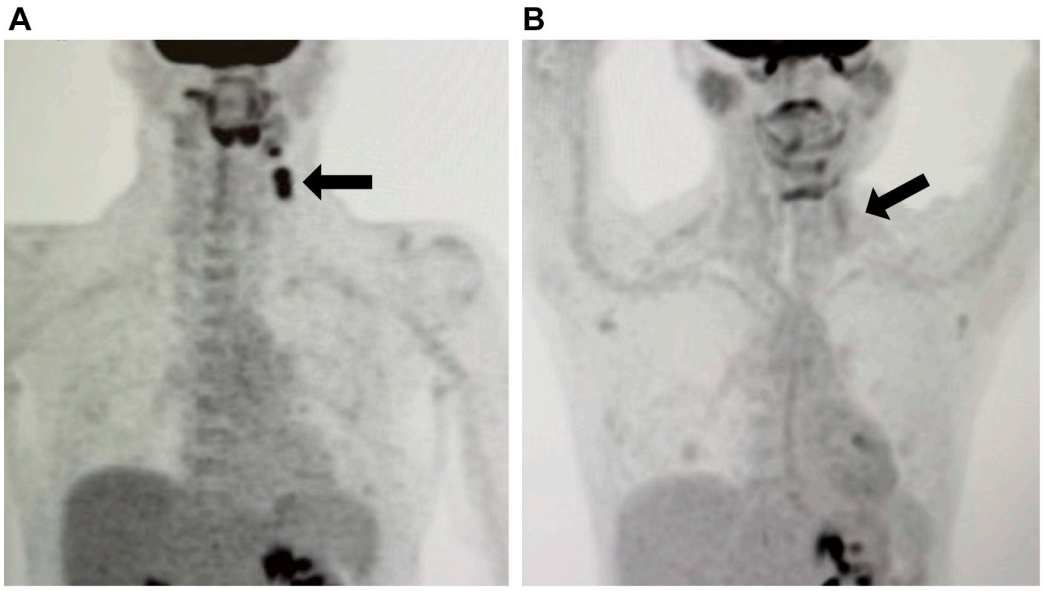

Figure 1. *Remission of recurrent metastatic squamous-cell carcinoma of the tongue as shown by [^{18}F]fluorodeoxyglucose (FDG)- positron emission tomography (PET)/computed tomography. (A) FDG uptake by the recurrence of squamous cell carcinoma in the left submandibular region following curative-intent surgery and subsequent chemotherapy on February 25th, 2025. (B) Disappearance of FDG uptake upon PET imaging after the incorporation of a low-methionine diet and oral recombinant methioninase combined with chemotherapy on October 30th, 2025.*

dissection on October 4th, 2023, with negative surgical margins. Three metastatic lymph nodes without extranodal extension were also resected. Postoperative radiotherapy was declined by the patient.

Local recurrence with rapid progression and skin invasion was diagnosed by [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET)/ computed tomography (CT) on April 5, 2024. The patient then received induction chemotherapy with paclitaxel (80 mg/m^2, administered weekly), carboplatinum (AUC 5, administered every 3 weeks) and cetuximab (400 mg/m^2 loading dose, followed by 250 mg/m^2 weekly) for two cycles, achieving rapid tumor shrinkage, followed by salvage surgery on July 10, 2024. Pathological analysis revealed one metastatic lymph node with extranodal extension. Postoperative chemoradiotherapy (66 Gy in 33 fractions) was administered to the tumor bed and bilateral neck from August to October 2024. A further local recurrence in the left submandibular region was confirmed by biopsy on February 25, 2025 (Figure 1A). Nivolumab (240 mg intravenously every 2 weeks) was initiated in March 2025 but produced no meaningful clinical response.

Therefore, paclitaxel (80 mg/m^2 weekly) plus cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly) was started in April 2025 along with methionine restriction. Methionine restriction consisted of a low-methionine diet (https://nutritionaloncology.net/home) combined with oral rMETase (5 mg orally twice daily).

Although the tumor showed significant regression, rapid shrinkage was complicated by treatment-related skin ulceration with exposure of the patient's titanium mandibular reconstruction plate. After four courses, treatment was de-escalated to cetuximab monotherapy (500 mg/m^2 every 2 weeks) starting on August 18, 2025, along with methionine restriction. Follow-up FDG-PET/CT on October 30, 2025, demonstrated no residual disease, and complete response was confirmed on November 11, 2025 (Figure 1B). No severe adverse events occurred during treatment, and no functional impairments such as dysphagia or speech disturbance were observed.

Ethics statement. The patient gave written informed consent for the present study.

Discussion

To our knowledge, the present case represents the first report of recurrent HNSCC that developed after curative-intent surgery and failure of standard therapies, including immune checkpoint inhibition, ultimately achieving complete remission through combining methionine restriction and chemotherapy. Sustained disease control was achieved following de-escalation to cetuximab monotherapy as previously published (24) combined with continued MR. Given that postoperative recurrence of HNSCC is associated with a reported 5-year survival rate of approximately 10-20%, the favorable outcome observed in the present patient is clinically meaningful (25).

Methionine restriction exploits a metabolic vulnerability of cancer cells characterized by their dependence on exogenous methionine for proliferation, a phenomenon termed methionine addiction or the Hoffman effect (17-20, 26-40). To translate this concept into clinical application, oral rMETase was developed as a dietary supplement aimed at reducing systemic methionine availability (21, 30). Extensive experimental data have demonstrated that methionine depletion suppresses tumor growth of diverse cancer types in both cellular and animal models (18, 19). Methionine restriction enhances the antitumor activity of cytotoxic chemotherapy, providing a strong biological rationale for combined treatment strategies (20, 29).

The present case suggests that adding methionine restriction to chemotherapy may provide a viable therapeutic option for patients with recurrent HNSCC for whom conventional treatments have been exhausted. Although interpretation is limited by the single-case nature of this report, the observed clinical response supports further evaluation of this approach. Larger case series and prospective clinical trials will be required to determine its reproducibility, safety, and long-term benefit.

Targeting methionine addiction may represent a broadly applicable strategy, as it addresses a fundamental metabolic hallmark shared by multiple cancer types (17-22, 26-40).

Conflicts of Interest

The Authors declare no potential conflicts of interest.

Authors' Contributions

TI collected the patient data and wrote the manuscript. RMH revised the manuscript. TS treated the patient. QH and SL produced recombinant methioninase. YM, BMK, JSK, TT critically read the manuscript.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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