Intra-arterial chemoradiotherapy for locally advanced buccal mucosal cancer in an elderly patient with multiple comorbidities: A case report

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Abstract
Background: The management of locally advanced oral cavity squamous cell carcinoma (LA-OCScc) in elderly patients with multiple comorbidities is difficult.

Case: We report the case of an elderly patient with buccal mucosal squamous cell carcinoma as well as chronic renal dysfunction, hepatic cirrhosis, rheumatoid arthritis, and metachronous diffuse large B-cell lymphoma. We performed radiation therapy (a total dose of 70 Gy in 35 fractions) and six cycles of intra-arterial chemotherapy with 40 mg/m² cisplatin per week.

After treatment, the tumor completely disappeared, and there was no recurrence or deterioration of comorbidities during the 12-month follow-up period.

Conclusion: Intra-arterial chemoradiotherapy may be a good treatment option for LA-OCScc in elderly patients with multiple comorbidities.

KEYWORDS
buccal mucosal cancer, cisplatin, comorbidities, intra-arterial chemoradiotherapy, squamous cell carcinoma

1 | INTRODUCTION

Head and neck cancer is a common malignancy that causes more than 300,000 deaths per year worldwide.1 Approximately 25% of patients with head and neck cancer are over the age of 70 years.2,3 Various prognostic factors of head and neck cancer have been reported. Several factors, such as age, comorbidity, and human papilloma virus status, often have an influence on initial treatment strategy.4–6

Surgery followed by postoperative chemoradiotherapy is the standard treatment for locally advanced oral cavity squamous cell carcinoma (LA-OCScc). Up-front surgery for LA-OCScc has been shown to provide a substantial survival benefit compared to definitive radiotherapy with or without chemotherapy in a small randomized trial7 and several retrospective studies.8–10 However, the number of patients with LA-OCScc receiving non-surgical treatment has been increasing.5 In particular, patients aged 75 years or older have received non-surgical treatment more often than younger patients.10

Concurrent chemoradiotherapy (CRT) is the most acceptable treatment approach for the non-surgical treatment of LA-OCScc. The standard treatment regimen consists of three cycles of cisplatin (100 mg/m²) administered on days 1, 22, and 43 during radiotherapy (70 Gy in 35 fractions).11,12 Since CRT improves survival outcomes achieved after radiotherapy alone, in addition to an increase in side effects, the management of toxicities has been important.13,14 Several studies have shown that elderly patients can achieve outcomes similar to those of younger patients who receive aggressive treatments.15,16
Nevertheless, elderly patients often receive less aggressive treatments, such as radiotherapy alone, compared with younger patients with the same disease status. This tendency is remarkable in elderly patients with multiple comorbidities. In the elderly, complications such as renal dysfunction have a significant impact on life expectancy; therefore, it is important to make aggressive treatment choices if the patient can tolerate the treatment.

In a randomized controlled phase 3 trial in patients with locally advanced unresectable head and neck cancer, intraarterial chemoradiotherapy (IA-CRT) was not superior to intravenous chemoradiotherapy (IV-CRT) in relation to outcomes, but rates of local control and overall survival were similar between the two groups. Superselective intraarterial chemotherapy (IA-CT) is divided into two types: selective arterial infusion through the femoral artery or retrograde selective infusion via the superficial temporal artery (STA) and/or occipital artery (OA). The former method is standard, but some studies have reported the risk of neurologic toxicity. In contrast, the conventional method of catheterization through the STA is rarely associated with neurologic toxicity, but results in inadequate selectivity in some patients in whom the tumor was supplied by multiple arteries. Our previous report described treating head and neck cancer with multiple tumor-feeding arteries with retrograde superselective IA-CT using an external carotid arterial sheath (ECAS) system. Supercselective IA-CT using the ECAS system can be performed in elderly patients with carotid artery stenosis. However, there is insufficient evidence to show the efficacy and safety of retrograde intraarterial chemotherapy with concurrent chemotherapy in elderly patients with multiple comorbidities. In this study, we report a case study using IA-CT with concurrent radiotherapy in an elderly patient with LA-OCSc as well as chronic renal dysfunction, hepatic cirrhosis, rheumatoid arthritis, and metachronous diffuse large B-cell lymphoma.

2 | CASE REPORT

A 76-year-old man was referred to Mie University Hospital due to exacerbation of swelling of the right buccal mucosa. He had a history of cirrhosis (Child-Pugh class B) and chronic renal dysfunction. He was taking prednisolone for rheumatoid arthritis. In addition, he had maintained complete response for 3 years after treatment with six cycles of the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone regimen for methotrexate-related malignant lymphoma (DLBCL). Physical examination revealed a mass of the right buccal mucosa (28 × 25 mm) and a mucosal lesion on the soft palate (Figure 1). He had redness and induration on the skin near the right corner of the mouth. Computed tomography (CT) with contrast showed an enhancing tumor in the right buccal mucosa, and the lesion was suspected to extend to the soft palate (Figure 2). Magnetic resonance imaging (MRI) revealed similar findings. An enhancing effect was observed on the skin near the right corner of the mouth, and skin infiltration was suspected. No infiltration of the mandible was observed. There were no findings suggestive of metastatic lymph nodes or distant metastases. Imaging studies and buccal mucosal biopsy indicated a buccal mucosal squamous cell carcinoma (cT4aN0M0, stage IVA).

If surgery were to be performed, it would have required extensive resection and subsequent reconstructive surgery, not just the extent of the tumor invasion. Problems such as plastic surgery, anesthetics, and postoperative functional impairment were also considered. Therefore, the patient requested IA-CRT. Sequential boost intensity-modulated radiotherapy was delivered at a total dose of 70 Gy. The gross tumor volume (GTV) included the primary tumor (GTVp) and clinically metastatic lymph nodes (GTVn). Although there were no lymph node metastases at the time of staging, GTVn was defined as lymph nodes that showed shrinkage as irradiation proceeded. The clinical target volume 1 (CTV1) included the GTVp plus a 5- to 10-mm margin and elective nodal regions (ipsilateral levels I to V and the contralateral levels I to IV). CTV2 included GTV plus a 5- to 10-mm margin. CTV3 included GTVn plus a 5-mm margin. Three planning target volumes (PTV1-3) were created that encompassed the corresponding CTV with a setup margin of 3 mm. Dose prescriptions were 40 Gy in 20 fractions for PTV1, 60 Gy in 30 fractions for PTV2 and 70 Gy in 35 fractions for PTV3. A catheter was inserted through the right superficial temporal artery and placed between the right facial and maxillary arteries (Figure 3). CT angiography and the arterial infusion of indigo carmine were performed to detect tumor-feeding arteries. His creatinine clearance was 45.5 ml/min and we planned to administer cisplatin 40 mg/m²/week. Sodium thiosulfate (STS; 16 g/m²) was used for neutralization. Cisplatin 65 mg was injected into the right facial artery (35–40 mg) and the right maxillary artery (25–30 mg). After the completion of the three courses, neutropenia grade
(Common Terminology Criteria for Adverse Events, version 5.0) was observed and the treatment was temporarily discontinued. After confirming the recovery of neutrophils, chemotherapy was resumed and six courses were administered. The overall treatment time was 65 days.

Regarding acute adverse events, neutropenia was the only adverse event with grade 3 or higher. No exacerbation of liver or renal function was observed during the course of treatment or after the end of treatment. After the end of treatment, the tumor shrank significantly, and visual inspection and imaging showed a complete response.
There were no symptoms of recurrent tumor or unexpected complications from treatment at the 12-month follow-up after the completion of intra-arterial chemoradiotherapy.

## DISCUSSION

Although the treatment of an elderly patient with head and neck tumor with multiple comorbidities is challenging, IA-CRT is one of the curative treatments for inoperable patients. Here, we applied IA-CRT to a patient with LA-OCScc who was difficult to treat curatively due to age and basic diseases such as chronic renal failure and hepatic cirrhosis.

The standard treatment for LA-OCScc is surgery and postoperative radiotherapy with or without chemotherapy. According to previous reports on treatment outcomes of surgery with postoperative CRT in elderly patients with head and neck cancer, the 3-year overall survival (OS) and local control (LC) rates were 64% and 79%, respectively. However, major surgery is less frequently offered to elderly patients because the incidence of medical complications is significantly increased due to the presence of degenerative conditions and comorbidities.

With respect to the postoperative quality of life in elderly patients with locally advanced head and neck cancer undergoing major surgery, Khafif et al. reported that oral function was decreased by surgical intervention more severely in the elderly patient group than in the younger group.

Concurrent CRT is the most acceptable nonsurgical treatment approach for LA-OCScc. In a meta-analysis of chemotherapy, Pignon et al. demonstrated an absolute OS improvement of 6.5% at 5 years after the addition of concurrent chemotherapy to radiotherapy. In a subgroup analysis, they noted a decreasing survival benefit of chemotherapy with age, specifically in patients who were 71 years old or older. By contrast, some studies showed similar outcomes with the same treatment between elderly and younger patients. Two retrospective studies that investigated large national databases reported conflicting conclusions regarding the benefit of the addition of chemotherapy to radiotherapy on survival in elderly patients. However, both studies suggested that comorbidities are an important prognostic factor. The Charlson comorbidity index (CCI) is a method of categorizing patients’ comorbidities. Other studies including patients with head and neck squamous cell carcinoma treated with curative intended radiotherapy found that an increased level of comorbidity increased the risk of death.

In this case, the CCI score was 7. The management of elderly patients with high CCI is controversial. Superselective IA-CT for LA-OCScc has the advantage of delivering a high concentration of chemotherapeutic agents to the tumor bed with fewer systemic toxic effects than systemic chemotherapy. Robbins et al. reported the use of intra-arterial infusion of high-dose cisplatin (150 mg/m², weekly for 4 weeks) combined with STS for systemic cisplatin neutralization and a high response rate of IA-CRT. A randomized controlled phase 3 trial in patients with locally advanced unresectable head and neck cancer showed that IA-CRT was not superior to IV-CRT in terms of locoregional control and survival. However, outcomes in the IA-CRT group were similar to those in the IV-CRT group, and in a subgroup analysis, there was a significantly higher local and locoregional control rate in the IA-CRT group for large (>30 ml) lateralized tumors. Some retrospective studies of IA-CRT reported good outcomes for LA-OCScc (Table 1). In a study of 134 patients treated with retrograde IA-CRT with weekly carboplatin or cisplatin, the 3-year LC and OS rates were 69% and 54%, respectively. Mitsudo et al. evaluated the treatment outcomes of 112 patients with stage III and IV OCScc treated with retrograde IA-CRT with daily cisplatin and weekly docetaxel and reported 5-year LC and OS rates of 79% and 71%, respectively.

With respect to elderly patients with OCScc, Hayashi et al. evaluated the treatment outcomes of 31 patients with stage III and IV OCScc treated with IA-CRT and reported 5-year LC and OS rates of 81% and 78%, respectively.

### Table 1: Local control and survival rates in patients with oral cancer treated with intra-arterial chemoradiotherapy in previous studies

| Author       | Number of cases | Oral cancer rate (%) | Age (range) | Local control rate | Overall survival rate |
|--------------|-----------------|----------------------|-------------|--------------------|-----------------------|
| Fuwa et al.  | 134             | 100                  | Median 67 (25–89) | 69%, 3 years       | 54%, 3 years          |
| Mitsudo et al. | 112            | 100                  | Median 59 (28–87) | 79%, 5 years       | 71%, 5 years          |
| Hayashi et al. | 31             | 100                  | Median 83 (80–88) | 81%, 3 years       | 78%, 3 years          |
| Rasch et al. | 118             | 17                   | Mean 55       | 76%, 3 years       | 51%, 3 years          |
outcomes of retrograde IA-CRT with daily cisplatin and weekly docetaxel in 31 patients and reported 3-year locoregional control and OS rates of 81% and 78%, respectively.31

In addition to being elderly, our patient had moderate renal dysfunction, liver cirrhosis, and a history of chemotherapy. A reduction in the dosage of cisplatin is recommended in the presence of renal dysfunction, and the risk of bone marrow toxicity was anticipated to be higher due to cirrhosis and previous chemotherapy. When using cisplatin, it has been reported that the risk of neutropenia is lower with doses of 30–40 mg/m² weekly compared to 100 mg/m² tri weekly.32,33 Additionally, the risk of exacerbating renal dysfunction can be reduced with STS. In this case, the patient was able to receive six cycles of IA-CRT at 40 mg/m² with STS. In regard to myelosuppression, grade 3 neutropenia was observed during the treatment period, whereas after treatment, neutrophils, hemoglobin, and platelets recovered to pre-treatment levels. The outcome of this treatment was that the tumor was controlled for 12 months after the completion of IA-CRT without impairing the patient’s quality of life, such as renal dysfunction and dysphagia.

In conclusion, radiotherapy combined with intra-arterial chemotherapy may be curative non-surgical treatment option for locally advanced oral cancer in elderly patients with multiple comorbidities.

AUTHOR CONTRIBUTIONS
Akito Taniguchi: Conceptualization (equal); writing – original draft (equal). Yutaka Toyomasu: Writing – original draft (equal). Akinori Takada: Writing – review and editing (equal). Takamitsu Mase: Resources (equal). Kazuto Kurohara: Resources (equal). Akito Taniguchi: Conceptualization (equal); writing

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CONFLICT OF INTEREST
The authors declare that they have no conflict of interest related to this study.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
This case report does not require institutional review board approval, as it only includes one patient.

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