Complete response of recurrent oral squamous cell carcinoma treated with cetuximab in combination with radiotherapy: A case series

TOMOFUMI NARUSE, KOHEI FURUKAWA, TARO MIYOSHI, KOTA MORISHITA, MITSUNOBU OTSURU and MASAHIRO UMEDA

Department of Clinical Oral Oncology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8588, Japan

Received June 27, 2022; Accepted August 31, 2022

DOI: 10.3892/ol.2022.13551

Abstract. Salvage surgery for recurrent oral squamous cell carcinoma (OSCC) often leads to a poor quality of life (QOL). The present study described three cases that resulted in favorable locoregional control with cetuximab in combination with radiotherapy (Cmab + RT). Case 1 had regional recurrence of OSCC at the lower right mastoid area 4 months after primary surgery. Case 2 had regional recurrence of OSCC at the parotid area 7 months after primary surgery. Case 3 had local recurrence of OSCC at the masticatory muscle and Rouviere's lymph nodes 1 year and 3 months after primary surgery. In all cases, Cmab + RT was performed, and disease-free survival was confirmed 4 months, 2 years and 6 months, and 10 months after Cmab + RT, respectively. Immunohistochemically, all resected tumors had no expression of 110-kDa catalytic subunit of class IA phosphatidylinositol 3-kinase (PI3Kp110α). In conclusion, if salvage surgery for recurrent OSCC results in a significantly low QOL, then shifting to chemoradiotherapy may be appropriate as a treatment strategy. In addition, strong evidence indicated that PI3Kp110α expression is associated with Cmab therapy efficacy.

Correspondence to: Dr Tomofumi Naruse, Department of Clinical Oral Oncology, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8588, Japan
E-mail: naruse12@nagasaki-u.ac.jp

Abbreviations: HNSCC, head and neck squamous cell carcinoma; RT, radiotherapy; Cmab, cetuximab; ICI, immune checkpoint inhibitor; QOL, quality of life; OSCC, oral squamous cell carcinoma; PI3Kp110α, 110-kDa catalytic subunit of class IA phosphatidylinositol 3-kinase; Cmab + RT, Cmab in combination with RT; CT, computed tomography; BSA, body surface area; MRI, magnetic resonance imaging; OS, overall survival; ORR, overall response rate; R/M, recurrent or metastatic; ORN, osteoradionecrosis

Key words: Cmab, RT, locoregional recurrence, PI3Kp110α, salvage surgery

Introduction

According to the National Comprehensive Cancer Network (NCCN) guidelines, treatment options for patients with locoregional recurrence of head and neck squamous cell carcinoma (HNSCC) without prior radiotherapy (RT) includes salvage surgery, RT combined with chemotherapy, or combination chemotherapy followed by RT (1). The classical chemotherapy treatment options include high-dose platinum plus 5-fluorouracil or cetuximab (Cmab) (1). Moreover, immune checkpoint inhibitors (ICIs), such as pembrolizumab with or without the platinum or EXTREME regimens, are recommended as category 1 therapies because of their effectiveness in very advanced HNSCC (2,3). Among the treatment options, salvage surgery with curative intent has shown a survival benefit (4-6). However, salvage surgery often results in a poorer quality of life (QOL) because of dysphagia or speech problems. Therefore, participating in multidisciplinary discussions regarding treatment options is recommended to maximize survival while preserving form and function (1). At present, no clear criteria exist for salvage surgery treatment. Since salvage surgery may result in a significantly lower QOL, then a shift to chemoradiotherapy as the treatment strategy might be appropriate. In our previous report regarding Cmab-containing chemotherapy, we suggested that high expression of the 110-kDa catalytic subunit of class IA phosphatidylinositol 3-kinase (PI3Kp110α) may play an important role in Cmab resistance, and PI3Kp110α is a predictor for Cmab therapy in recurrent and metastatic oral squamous cell carcinoma (OSCC) (7).

Based on the treatment strategy in our department, patients commonly undergo surgery with or without adjuvant RT or concurrent chemoradiotherapy against primary OSCC according to the NCCN guidelines (1). We describe our experiences of three patients who received Cmab in combination with RT (Cmab + RT) for loco-regional recurrent OSCC and achieved long-term survival of 5 years or more while maintaining the QOL. We also reported PI3Kp110α findings from an immunohistochemical study to clarify the validity of our previous report (7).

Case report

Case 1. A 63-year-old man who was complaining of a painful mass at the right side of his tongue was referred to Nagasaki University Hospital (Nagasaki, Japan) in March 2017. Intraoral examination revealed a 48x35 mm elastic and hard mass with a central ulceration involving the right tongue (Fig. 1A). Contrast-enhanced axial computed tomography (CT) revealed a poorly marginated lesion and right regional lymph node involvement (Fig. 1B and C). The depth of clinical invasion was 27 mm. He was diagnosed with SCC of the tongue (cT4aN1M0 stage IVA) based on the clinical and biopsy findings. Under general anesthesia, the patient underwent subtotal glossectomy, modified radical neck dissection, and reconstruction with a pectoral major musculocutaneous flap. Pathological findings of the primary tumor showed keratinizing tumor cells that had relatively round or cord-like tumor nests with deeply stained irregular nuclei, which infiltrated the submucosa and surrounded the deep muscle layer of the tongue (Fig. 2). However, 4 months after surgery, regional recurrence was noted at the lower right mastoid region contacting the cervical vertebrae processus transversus. Although salvage surgery was considered, the patient underwent Cmab + RT because extensive resection would result in dysphagia and lead to a poorer QOL. RT was administered at a total dose of 66 Gy. Concomitant RT was administered at 2 Gy/day for 6 days/week. Cmab was administered for 6 courses at a dose of 400 mg/m^2 of body surface area (BSA) for the first injection followed by 250 mg/m^2 BSA/week thereafter. Among the adverse events, grade 2 radiation dermatitis, oral mucositis, and acne like rash were observed. All the adverse events were manageable. Disease-free status was confirmed by enhanced CT 4 months after Cmab + RT (Fig. 3A-C), and there were no signs of recurrence or progression 5 years after Cmab + RT.

Case 2. A 77-year-old woman who was complaining of a painful mass at the right buccal mucosa was referred to Nagasaki University Hospital in May 2015. History revealed that she had undergone neoadjuvant chemotherapy [cisplatin (117.75 mg)/tegafur/gimeracil/oteracil potassium (2,640 mg)], marginal mandibulotomy, and radical neck dissection for SCC of the right mandible (cT4N1M0 stage IVA) 6 years ago in our department. Intraoral examination revealed a 27x18 mm elastic and hard mass with a central ulceration at the right buccal mucosa. Contrast-enhanced axial magnetic resonance imaging (MRI) revealed a poorly marginated lesion and left regional lymph node involvement. The clinical invasion depth was 14 mm. She was diagnosed with SCC of the buccal mucosa (cT2N2bM0 stage IVA) based on the clinical and biopsy findings. Under general anesthesia, the patient underwent tumorectomy of the buccal mucosa, modified radical neck dissection, and reconstruction with a forearm flap. SCC of the buccal mucosa was diagnosed pathologically. However, regional recurrence was noted at the parotid lymph node 7 months after surgery. Although salvage surgery was considered, she refused this treatment as it may result in facial nerve paralysis and xerostomia, which may lead to a poorer QOL; she instead underwent Cmab + RT. RT was administered at a total dose of 66 Gy. Concomitant RT was

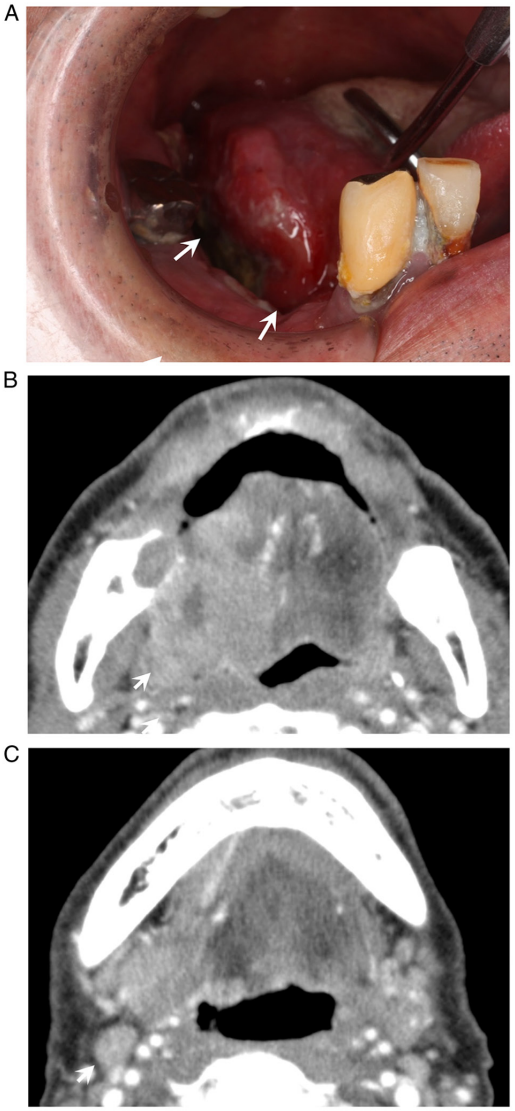

Figure 1. Representative clinical and imaging findings in Case 1. (A) Intraoral examination revealed an elastic and hard mass with a central ulceration involving the right tongue (white arrow). (B) Contrast-enhanced axial computed tomography showed a poorly marginated lesion (white arrow) and (C) right regional lymph node involvement (white arrow).

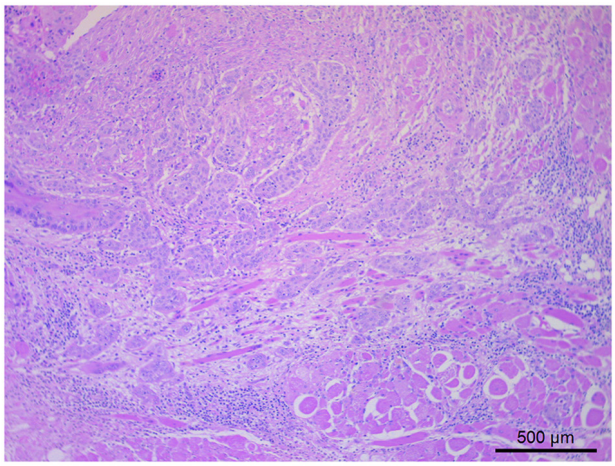

Figure 2. Pathological findings of the tumor revealed keratinizing tumor cells with relatively round tumor nests and deeply stained irregular nuclei. Magnification, x100.

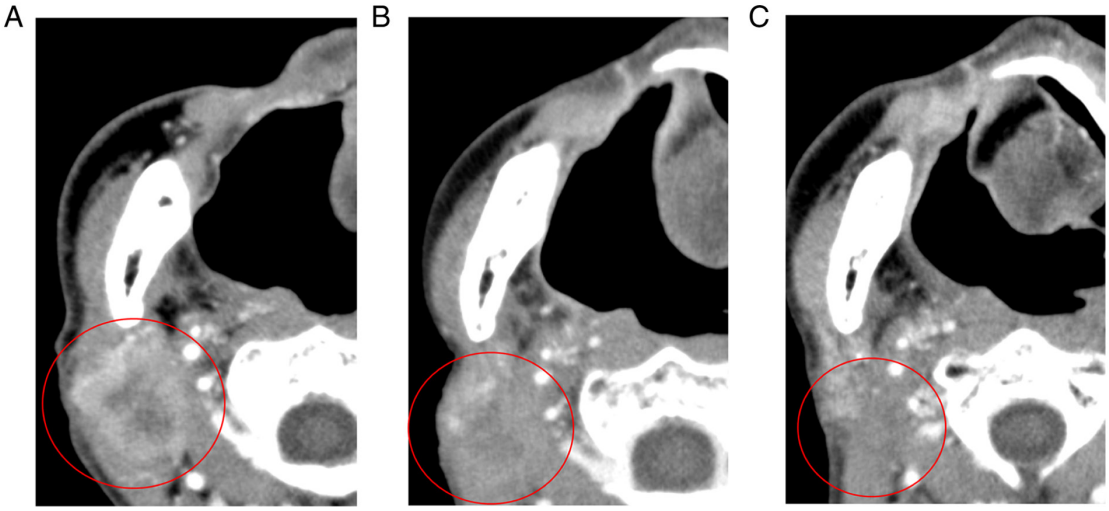

Figure 3. Regional recurrent oral squamous cell carcinoma in Case 1 (red circle). (A) Before Cmab + RT, (B) end of Cmab + RT, and (C) 4 months after Cmab + RT. Cmab, cetuximab; RT, radiotherapy.

administered at 2 Gy/day for 6 day/week. Cmab was administered for 6 courses at a dose of 400 mg/m^2 of BSA for the first injection followed by 250 mg/m^2 BSA/week thereafter. In the adverse events, grade 2 radiation dermatitis, grade 3 oral mucositis and grade 2 acne like rash were observed. All the adverse events were manageable. Disease-free status was confirmed using enhanced MRI 2 years and 6 months after Cmab + RT (Fig. 4A-C), and there were no signs of recurrence or progression 6 years after Cmab + RT.

Case 3. A 71-year-old man who was complaining of a painful mass at the left mandible was referred to Nagasaki University Hospital in March 2015. Intraoral examination revealed a 15x15 mm elastic and hard mass with a central ulceration at the lingual side of left retromolar region. Contrast-enhanced axial MRI revealed a poorly marginated lesion and left regional lymph node involvement. The clinical invasion depth was 8 mm. The patient was diagnosed with SCC of the mandibular gingiva (cT2N2bM0 stage IVA) based on the clinical and biopsy findings. Under general anesthesia, the patient underwent marginal mandibulotomy and modified radical neck dissection. SCC of the mandibular gingiva was pathologically diagnosed. However, local recurrence was noted at the masticator space and regional recurrence was noted at the Rouviere's lymph nodes 1 and 3 months after surgery, respectively. Although salvage surgery was considered, the patient underwent Cmab + RT because the lesion was unresectable. RT was administered at a total dose of 66 Gy. Concomitant RT was administered at 2 Gy/day for 6 day/week. Cmab was administered at a dose of 400 mg/m^2 of BSA for the first injection followed by 250 mg/m^2 BSA/week thereafter. After RT, Cmab was maintained for approximately 2 years because of a residual, but localized tumor in the masticatory muscle. In the adverse events, grade 1 radiation dermatitis, grade 3 oral mucositis, and grade 1 acne like rash were observed. All the adverse events were manageable. Disease-free status was confirmed using enhanced MRI 10 months after RT (Fig. 5A-C), and there were no signs of recurrence or progression 5 years and 9 months after RT.

Immunohistochemical staining and evaluation. Immunohistochemical staining was performed by using the EnVision method (EnVision+; Dako), as previously described (7). For the assay, specimens were obtained immediately before Cmab + RT. Because neoadjuvant and adjuvant chemotherapy were not administered to all the patients before Cmab + RT, paraffin-embedded sections of the resected primary tumor specimens were selected. PI3Kp110α (dilution 1:400) rabbit polyclonal primary antibody from Abcam was used. Negative controls were prepared by replacing the primary antibody with phosphate-buffered saline. Normal oral mucosal specimens from three healthy individuals were used as positive controls.

Among the three patients, no PI3Kp110α expression was detected in all patients (Fig. 6A-L). High PI3Kp110α expression in a case of OSCC described in our previous study (7) was shown in Fig. 6M. Our previous study revealed that high PI3Kp110α expression was significantly associated with cetuximab resistance (7). In these results, weak PI3Kp110α expression showed Cmab sensitivity.

Discussion

The goal of this article was to describe the usefulness of Cmab + RT and assess the predictors of PI3Kp110α for Cmab therapy in locoregional recurrence of OSCC. Treatment options recommended for patients with locoregional recurrence of HNSCC without prior RT include salvage surgery, RT combined with chemotherapy, or combination chemotherapy followed by RT (1). Salvage surgery with curative intent has shown survival benefit (4-6). However, salvage surgery often lowers the patient's QOL. Horn *et al* reported that impaired swallowing and speech lowered the overall QOL 3 months after salvage surgery, although the patients recovered within 5 years (8). Recently, the development of molecular targeted drugs and ICIs has resulted in improved patient survival and QOL, which have been turning points in the treatment strategy for locoregional HNSCC. Therefore, if salvage surgery will lower a patient's QOL, chemoradiotherapy should be performed instead.

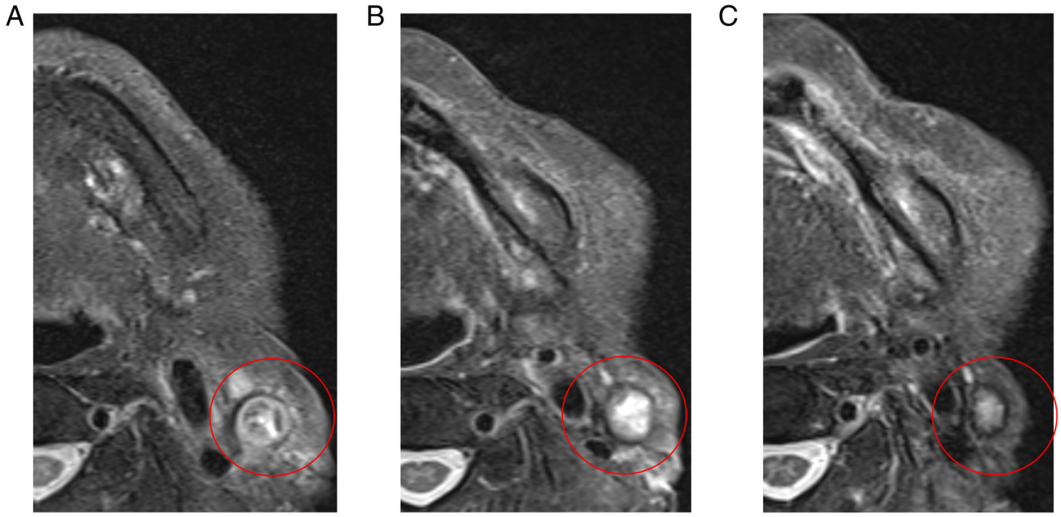

Figure 4. Regional recurrent oral squamous cell carcinoma in Case 2 (red circle). (A) Before Cmab + RT, (B) end of Cmab + RT, and (C) 2 year and 6 months after Cmab + RT. Cmab, cetuximab; RT, radiotherapy.

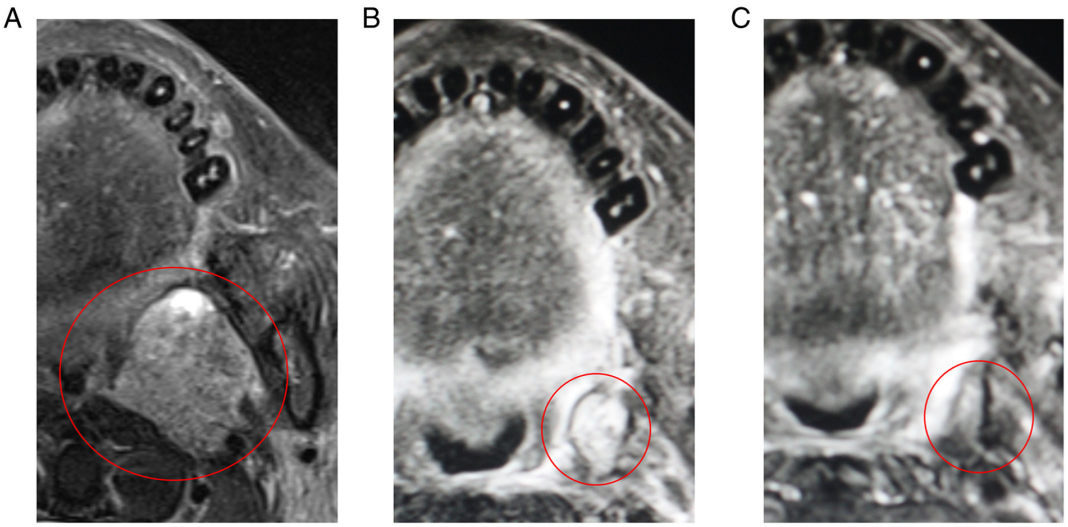

Figure 5. Regional recurrent oral squamous cell carcinoma in Case 3 (red circle). (A) Before Cmab + RT, (B) end of RT, and (C) 10 months after RT. Cmab, cetuximab; RT, radiotherapy.

We experienced three cases of favorable locoregional control against locoregional recurrence of OSCC with Cmab + RT. In a prospective study of locoregional recurrence of HNSCC, Hecht *et al* reported that Cmab + RT had superior progression-free survival and overall survival (OS) compared to Cmab alone, with a 1-year OS of 53% (9). Other two studies have reported that the 1-year OS of Cmab + RT were 44 and 47.5%, respectively (10,11). The overall response rate (ORR) in these reports was 16-58%, which was different from previous study (9-11). In contrast, the 1-year OS of salvage surgery was approximately 50% (5,6) and 1-year OS of chemotherapy with Cmab (EXTREME regimen and Cmab plus paclitaxel) was approximately 40% in recurrent or metastatic (R/M) OSCC (12,13). Meanwhile, the ORRs for the EXTREME regimen and Cmab plus paclitaxel were 46.2 and 48.4%, respectively. More recently, pembrolizumab was approved as first-line treatment for patients with R/M HNSCC (1); its 1-year-OS with immunotherapy (pembrolizumab alone or with chemotherapy) is 49-57% (2). However, in a subgroup analysis of patients with locoregional recurrence, the efficacy of pembrolizumab alone did not differ from the EXTREME regimen in selected patients (programmed death ligand-1 combined positive score ≥1) (2). Although the comparison of different treatment modalities was challenging because of differences, such as regions of recurrent OSCC and previous therapy, Cmab + RT was not inferior to other treatments for locoregional recurrence of OSCC.

Regarding lowered QOL, late adverse events after RT, such as impairments in swallowing and eating, and salvage surgery result in a lower QOL. Osteoradionecrosis (ORN) of the jaw is a severe late adverse event of RT that occurs in the head and neck region. ORN interferes with the patient's daily activities due to persistent pain, drainage from the exposed bone, trismus, and eating disorders, resulting in a poor QOL. Kojima *et al* reported that ORN developed in 30 of 392 patients (7.7%) administered with 50 Gy of RT in the head and neck region (14). The standard therapy for ORN

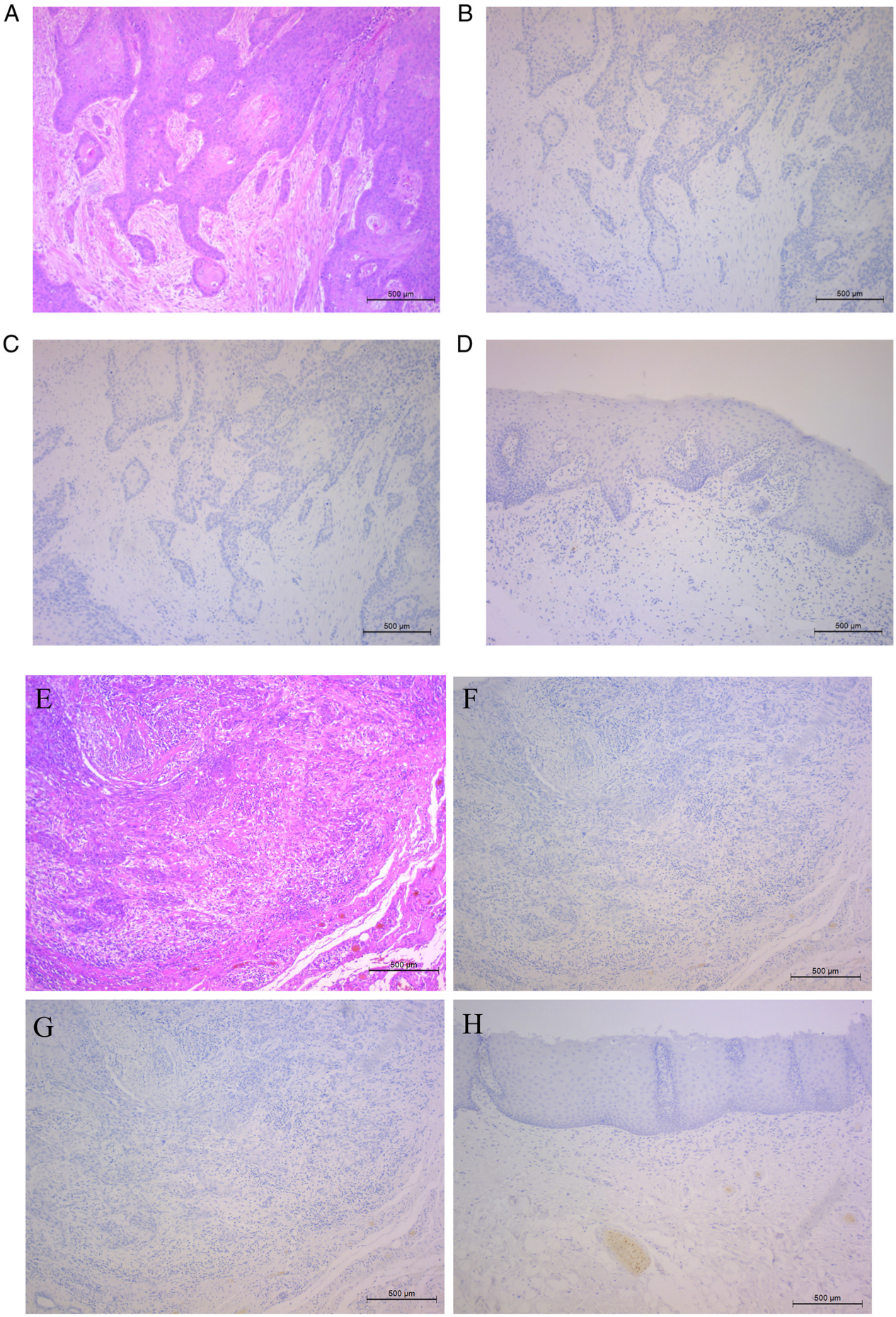

Figure 6. Continued.

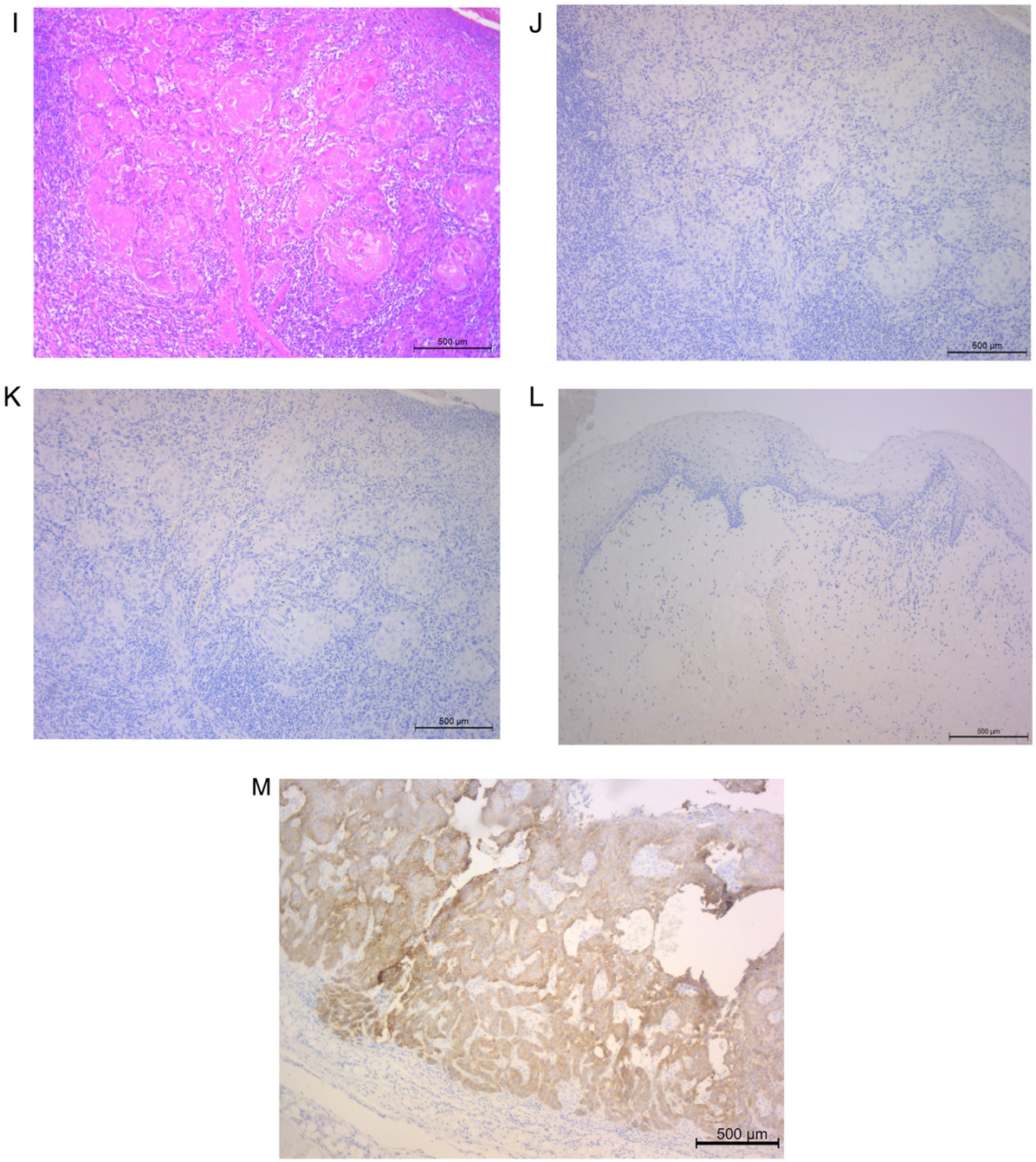

Figure 6. Representative immunohistochemical features of PI3Kp110α expression in OSCC. No expression was observed in Case 1; (A) H&E stain; (B) negative control; (C) PI3Kp110α; (D) positive control. No expression was observed in Case 2; (E) H&E; (F) negative control; (G) PI3Kp110α; (H) positive control. No expression was observed in Case 3; (I) H&E; (J) negative control; (K) PI3Kp110α; (L) positive control). (M) High PI3Kp110α expression in OSCC. Magnification, x100. PI3Kp110α, 110-kDa catalytic subunit of class IA phosphatidylinositol 3-kinase; OSCC, oral squamous cell carcinoma; H&E, hematoxylin and eosin.

has not yet been established; however, it sometimes requires extensive jawbone resection. Although ORN did not develop in our patients, periapical periodontitis and tooth extraction after radiotherapy are independent risk factors for ORN, which should be monitored in patients receiving RT in the head and neck region (14,15).

As a predictor of response to Cmab therapy, Argiris *et al* (16) has reported that vascular endothelial growth factor (VEGF) and interleukin (IL)-6 were identified as potentially useful serum biomarker predictors. In addition, Oliveras-Ferraros *et al* (17) reported that interferon/STAT1 and neuregulin signaling pathways are predictors of Cmab efficacy in KRAS wild-type squamous carcinomas. Cmab promotes epithelial-to-mesenchymal transition (EMT), which Cmab resistance is associated with. In previous reports, the association between increased expression of EMT markers and Cmab resistance have been reported (18,19). We have previously reported that based on the immunohistochemical staining of recurrent tumors, as in this case, before and after long-term Cmab administration, increased expression of EMT markers was observed (20). In addition, we have also previously suggested that inhibition of PI3Kp110α was not only

a good predictor for Cmab therapy, but that it also inhibits the potential of Cmab-resistant cells to undergo EMT in OSCC (7). Therefore, we believe that PI3Kp110α is one of the best useful predictors for Cmab therapy in OSCC. In our three cases, either no or weak expression of PI3Kp110α was observed, resulting in better clinical outcomes. Therefore, this case series provides strong evidence of the association between PI3Kp110α expression and Cmab resistance, as was reported in our previous study. Bonner *et al* (21) reported that Cmab-induced moderate or severe skin rash is associated with better survival. In our case series, two patients with severe oral mucositis were observed, but in all the patients with adverse events (radiation dermatitis and acne like rash), these were mild or moderate, and there was no relationship between adverse events and PI3Kp110α expression.

A potential limitation of our experience is that only three cases were reported. Additionally, patient backgrounds, such as the regions of recurrent OSCC, previous therapies, and tumor heterogeneity, differed among the patients. Moreover, we did not compare the efficacy of Cmab + RT with that of other therapies (salvage surgery or chemotherapy). Therefore, our findings should be interpreted with caution.

In conclusion, our experience suggests that if salvage surgery for recurrent OSCC will result in a significantly low QOL, then shifting to chemoradiotherapy is appropriate as one of the treatment strategies. Furthermore, our experience provides strong evidence that PI3Kp110α expression is associated with Cmab therapy efficacy.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

TN, KF, TM, KM, MO and MU contributed to the conception and design of the study. Clinical data were collected by TN, TM and KM. Data analysis for the immunohistochemical study was performed by TN, KF and MU. TN and MU confirm the authenticity of all the raw data. The first draft of the manuscript was written by TN, and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This immunochemical study was approved by the independent ethics committee of Nagasaki University Hospital (approval no. 20042012). Patients were given the opportunity to opt out of participation in the research involving the immunohistochemical study of tissues.

Patient consent for publication

Written informed consent for publication was obtained from the three patients.

Competing interests

The authors declare that they have no competing interests.

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