Case Series

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Reconstructive surgery and adjuvant radiotherapy for the multimodal approach in oral cancer: a single cancer centre experience

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Introduction and importance: Ablative surgery for oral cancer, irrespective of the histological subtype, causes large tissue defects, functional and aesthetic damage. Microsurgical free flaps have been widely used in reconstruction after resection, with satisfactory success rates in conjunction with adjuvant radiotherapy (RT). This study aims to describe our clinical institutional experience based on the multimodal treatment performed in four cases diagnosed with oral squamous cell carcinoma with the use of different microvascular free flaps and RT.

Case series presentation: Four patients underwent reconstructive microsurgery after surgical resection of oral cancer, using three types of free flap: radial forearm fasciocutaneous, osteomyocutaneous fibular, and anterolateral thigh musculocutaneous flaps; RT was performed in Case 2 and Case 3. In the period of 3 years after microsurgical reconstruction and RT, flaps remain clinically stable without failure signs in full patients submitted to multimodal treatment.

Clinical discussion: After resection of oral carcinomas, extensive tissue defects can be successfully treated with reconstructive microsurgery using different types of microvascular free flaps. RT for locoregional control is a feasible option and did not seem to interfere with the survival of flaps.

Conclusion: An enhance long-term follow-up to assess overall and disease-free survival rates and quality of life must be carried out; however, cohort studies would be necessary for better understanding of the role of each treatment in the multimodal scheme.

Keywords: adjuvant radiotherapy, mandibular reconstruction, microsurgical free flaps, oral squamous cell carcinomas, reconstructive surgical surgery

Introduction

Head and neck cancer (HNC) is ranked the sixth most common malignant neoplasm worldwide and the histological subtype squamous cell carcinoma (SCC) accounts for ~90% of oral cancers[1]. Its incidence in the gingival mucosa is rare, and very little attention has been addressed to this specific location[2].

HIGHLIGHTS

- Microsurgical reconstruction is a feasible treatment modality after surgical removal of oral cancer.
- Different free flaps for oral and maxillofacial reconstruction are more often used after the removal of Oral squamous cell carcinoma lesions.
- It is known that multimodal treatment is the best option to treat local advanced oral cancer and reconstructive surgery is essential to be performed for further oral and maxillofacial rehabilitation.

Oral squamous cell carcinoma of the gums (OSCCG) represents about 25% of the cases of oral squamous cell carcinoma (OSCC)[3], with clinical and pathological features that vary according to the different world regions[2]. OSCCG has greater predilection for the elderly, with a mean age over 60 years, and frequently involves the mandibular gingival mucosa[2,4]. Whereas, verrucous oral carcinoma (VOC) is a less frequent variant, responsible for 2–12% of all oral carcinomas[3,4].

Clinically, OSCCG can be observed as an erythematous, leucoplakia or mixed lesion, with an exophytic, verrucous or ulcerated appearance, associated with tooth loosening, oedema, lip numbness and painful symptoms[2,4]. Moreover, patients with OSCCG often experience rapid bone marrow infiltration, which increases the chances of distant and locoregional metastases, and

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reduces the overall survival (OS) and disease-free survival (DFS) rates. Conversely, VOC is shown as an exophytic lesion, of slow growth and well located, with verrucous nipple lesions or a thick and painless white plaque with a cauliflower appearance, which are observed in the region of the buccal mucosa, residual alveolar gingival ridge, tongue, lip and floor of the mouth, with a higher incidence in elderly patients and lower rates for metastatic cancer[5–7].

The gold standard therapeutic approach is mainly surgical, based on marginal or segmental resection of the jaws with safety margins, either associated or not with selective neck dissection and postoperative radiotherapy (RT) and/or chemotherapy. Multimodal treatments have mainly been guided by the extension and initial staging of the lesion[2,7]. Other studies conducted by Niu *et al.*[2]. and Yang *et al.*[3]. observed 5-year OS rates of 72% and 57%, respectively, in cases of involvement of the mandibular and the maxilla gingiva, respectively.

Surgical resections promote large tissue defects, with functional and aesthetic damage. Thus, reconstructions with the placement of screw-retained plates have become a feasible option for oral and maxillofacial rehabilitation of these patients[2,8], Extensive palatal-maxillary defects resulting from surgical resection in the hard or soft palate region imply a high rate of morbidity, psychological and functional alterations such as dysphagia, nasal regurgitation of food, poor masticatory function, hypernasal speech[9,10], and loss of support for mid-facial soft tissues. Oral rehabilitation is essential and aims to replace the anatomical limits between the oral and nasal cavity and restore the functions of the stomatognathic system[9,10]. Therefore, the use of microvascular flaps and obturator prostheses are widely used for rehabilitation of palatal-maxillary defects, with satisfactory prognosis[11].

Several variations of microvascular flaps have been described in the literature for extensive tissue reconstruction, with predictable results as regards low complications and clinical success rates exceeding 90%[12]. Reconstructions from a radial forearm, fibular, lateral arm, anterolateral thigh flaps, among others, have been widely used[2,8,12]. When these post-surgical reconstructions are successful, they promote substantial improvements in the quality of life of patients and are associated with an increase in their OS, especially in advanced stages[8].

This study aimed to describe our institutional experience based on the clinical, imaging, histopathological and therapeutic features in the multimodal management of four cases diagnosed with OSCC emphasizing on microsurgical reconstruction using different microvascular free flaps and RT performed.

Case series presentation

This is a retrospective study presented as non-consecutive case series based on clinical, histological, and therapeutic analysis of patients diagnosed by OSCC and treated at Single Cancer Center in 2020. Moreover, we present the following article in accordance with the PROCESS reporting checklist[13]. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee (s) and with the Helsinki Declaration (as revised in 2013). The number protocol for ethical approval was 4.930.402/ RC101/21 by our Institutional Committee. Written informed consent was obtained from the patients for publication of this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Case 01

A 82-years-old man, who was diagnosed with multiple papillomatous lesions in the region of the buccal mucosa and on the left lateral border of the tongue, presented to our institution with the complaint of relapse of the lesions after he had undergone surgical resection in December 2020. After a new biopsy performed, the anatomical pathology analysis confirmed the diagnosis of VOC. Treatment was complete surgical resection, based on its initial clinical staging (cT1N0M0). Thus, an extensive glossectomy extending to the region of the lower lip mucosa was performed, (Fig. 1A, B) and microsurgical reconstruction with a forearm flap in order to obtain a soft tissue gain and thus enable further oral and maxillofacial rehabilitation to be performed (Fig. 1C). Histopathological examination of the specimen confirmed the diagnosis of well-differentiated VOC with lateral extension of 1.0 cm and infiltration depth of 4.0 mm, without perineural or lymph vascular invasion. Due to surgical margins free of neoplasm (> 5 mm) no adjuvant therapy was indicated.

Case 02

A 62-years-old man, diagnosed with OSCC of the tongue, with clinical staging of cT4aN2bM0, who had been treated with RT concomitantly with chemotherapy in 2015. RT was performed using the three-dimensional conformal technique, with a total dose of 70Gy delivered in the tumour bed and positive lymph nodes in 35 fractions, and 44Gy in the supraclavicular fossa and non-involved cervicofacial areas, in 22 fractions. (Fig. 2A-D). After a new biopsy in 2019, a relapse of the lesion was confirmed. Therefore, salvage hemimandibulectomy plus glossectomy (Fig. 3A, B), with selective supra-omohyoid (SOH) neck dissection from levels I–III was performed on the right side. In addition, microsurgical reconstruction was performed with the use of an osteomyocutaneous fibular flap (Fig. 3C, D), and screw-retained titanium plate used for repositioning (Fig. 3E, F). The histological examination showed a well-differentiated OSCC with an infiltration depth of 6.0 mm, without perineural or lymphovascular invasion, but with surgical bone margins involved with neoplasia. At the multidisciplinary medical (Tumor Board) reunion, the decision was made to perform adjuvant RT by means of an institutional protocol for re-irradiation of the mandibular smooth muscle tumour of uncertain malignancy cells with higher potential of infiltration. The intensity modulated radiation therapy (IMRT) technique was performed and 35Gy in 5 fractions were given every other day, and treatment was completed without locoregional complications (Fig. 4A-D).

Case 03

A 75-years-old man patient complained of an ulcerated lesion in the mandibular gingiva on the left side, with bone exposure, and extending to the ipsilateral skin region, associated with chronic trauma caused by a poorly adapted prosthesis. After clinical, imaging and biopsy performed in November 2020, the diagnosis of OSCC was confirmed as being a cT4N0M0. The medical chart showed a previous history of stomach adenocarcinoma diagnosed in 2014 and treated in 2015. The patient underwent three cycles of neoadjuvant chemotherapy (Taxol + Cisplatin-CDDP)

Figure 1. Microsurgical reconstruction after ablative surgery for removal of verrucous carcinoma of mandibular gingiva. (A–C) Show the phases after tumour removal, in which the microsurgical forearm flap was used.

and complete surgical resection, a left segmental mandibulectomy extending to the skin and ipsilateral masticatory space, with selective neck dissection of I–III supra-omohyoid lymph nodes was performed in April 2021 (Fig. 5A, B). Microsurgical reconstruction was performed with the anterolateral thigh (ALT) flap (Fig. 5C, D) for the purpose of further oral and maxillofacial rehabilitation of the area with titanium bone reconstructive plate, screws and dental implants with overdenture as recommended (Fig. 5E, F).

Histopathological analysis showed moderate cell differentiation, an infiltration depth of 2.0 cm, with perineural invasion and cortical bone infiltration. Surgical margins were free of neoplasia.

RT was administered with the IMRT technique and 60Gy delivered to the tumour bed, 54Gy in the lymph nodes levels Ib–III on the left side, following the trajectory of the mandibular branch of the trigeminal nerve (V3) to the skull base, divided into 30 sessions (Fig. 5G, H). During RT sessions, the prevention of radiation-induced mucositis was instituted with the use of a photobiomodulation protocol (low level laser therapy) in the entire oral mucosa and structures adjacent to the positioned flap, throughout the entire period of RT.

Case 04

A 68-years-old woman, complained of pain in the posterior area of hard palate associated with a circumscribed lesion. Previously, she had undergone total glossectomy with radical neck dissection on the right side, SOH (I–III levels) on the left, and microsurgical reconstruction with a pectoralis major flap, after removal of OSCC of the tongue performed in March 2017, with clinical and pathological stages established as being cT4aN2cM0 and pT4apN2aM0, respectively. Three years later, in June 2020, she was submitted to a new biopsy in a cauliflower-like ulcerated lesion in the hard palate that was diagnoses as being papillomatous. After a new biopsy in the hard palate in February 2021, the diagnosis of OSCC was confirmed. The therapy was based on total maxillectomy extending to the soft palate (Fig. 6A-C), performed in April 2021 and microsurgical reconstruction was performed using pectoralis flap. Histopathological analysis showed well-differentiated OSCC cells, with an infiltration depth of 1.5 mm, pathological staging of T4N0 and safety margins; therefore, no adjuvant therapy was indicated. At present, the patient is being followed-up by our Department of Nutrition and Speech Therapy due to her moderate condition of dysphagia.

Histopathological analysis was performed in all cases as described in Fig. 7A-D. In all cases, the 3-year postoperative examination showed a satisfactory clinical condition of the flaps positioned (Fig. 8A-G).

Discussion

HNC continues to be a challenging disease to treat, despite screening and diagnostic techniques having overcome some limitations, and in these last few years this field has shown improvements as regards the establishment of prognostic and predictive factors associated with the disease[14,15]. OSCC is the histological subtype frequently diagnosed, and its incidence varies according to the anatomical topography involved[1,8,14]. Gingival carcinoma is rare, often difficult to diagnose, and leads to delays in instituting its proper management[2,4].

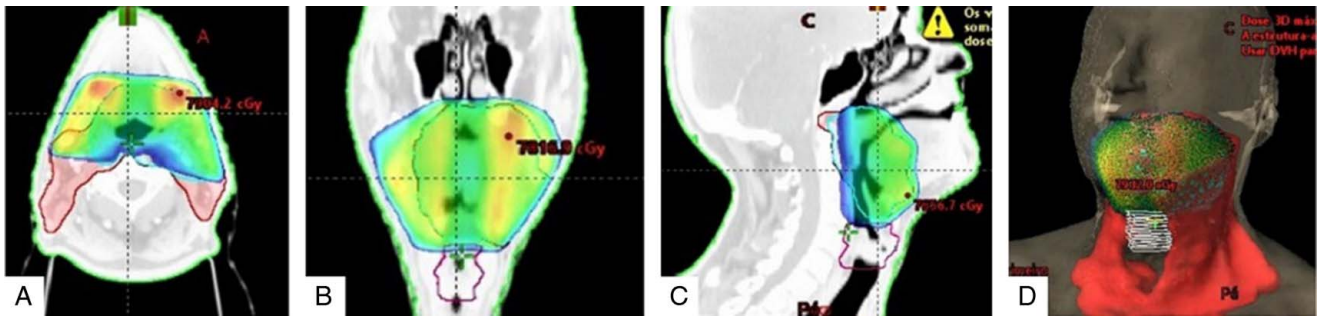

Figure 2. First cycle of radiotherapy (RT) performed. (A–D) RT with the three-dimensional conformal technique performed with dose distribution between 7000 and 7932 cGy.

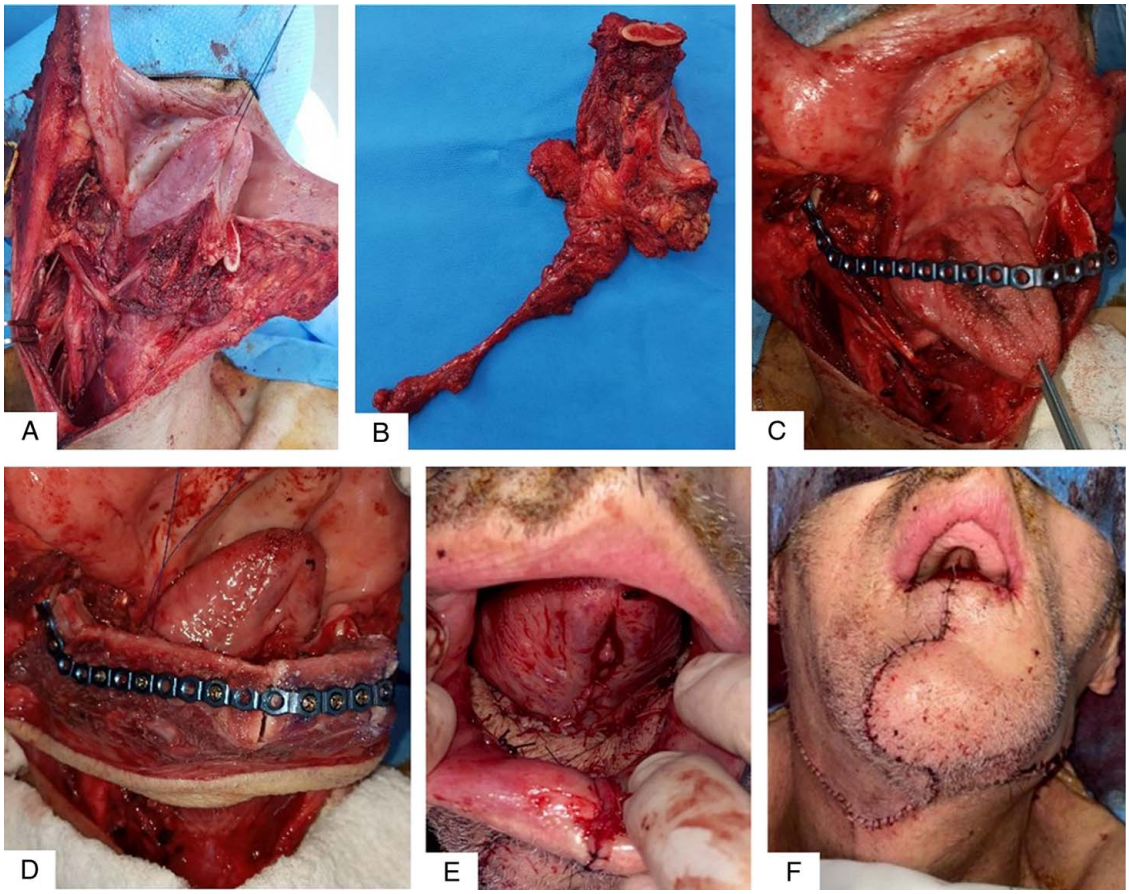

Figure 3. Microsurgical reconstruction of relapse of oral squamous cell carcinoma in the mandible. In (A, B) the tumour bed is shown after segmental mandibulectomy on right side. (C, D) Show the placement of a screw-retained titanium plate for mandibular contour and fixation of the fibular flap. In (E, F) the intra and extraoral examination in the postoperative period is shown after flap placement.

Differential diagnosis with odontogenic and non-odontogenic lesions and infections such as pyogenic granuloma, viral and fungal lesions and those associated with endo-periodontal origin have been described[2,4]. Clinical and pathological stages according to the current classification of HNC tumours have become useful for making therapeutic decisions, which range from medium to extensive surgical resections, with the aim of guaranteeing free margins after removal and, consequently, to increase in the OS, DFS and progression-free survival rates[15]. While adjuvant therapies are associated with better local control for avoiding locoregional relapses, and distant metastases[16].

Tumours in early stages are, in general, treated with surgery and/or radiotherapy, commonly with high rates of OS and DFS. For advanced tumours, other therapeutic modalities such as immunotherapy or chemoradiation offer better rates of locoregional control, OS, DFS and decrease in metastatic lesions. Some

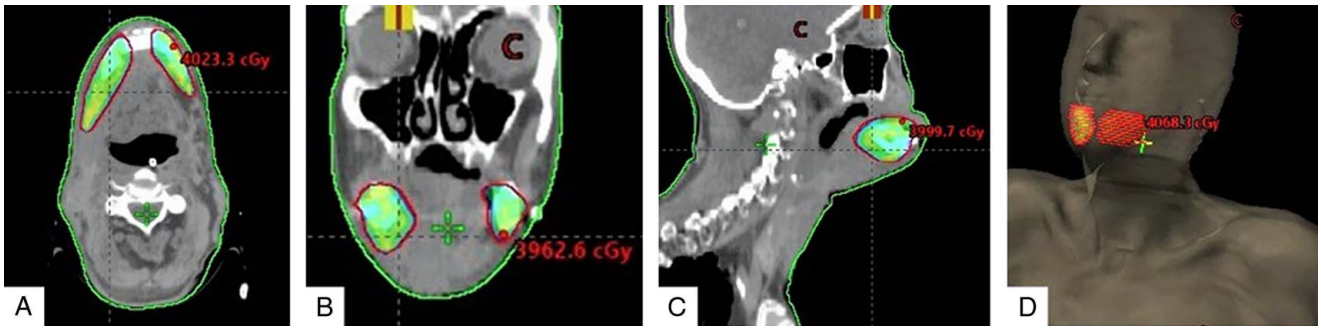

Figure 4. (A–D) Re-irradiation using Intensity modulated radiation therapy technique with a dose distribution between 3500 and 4068.3cGy, applied to the mandibular smooth muscle tumour of uncertain malignant potential infiltrated by the tumour.

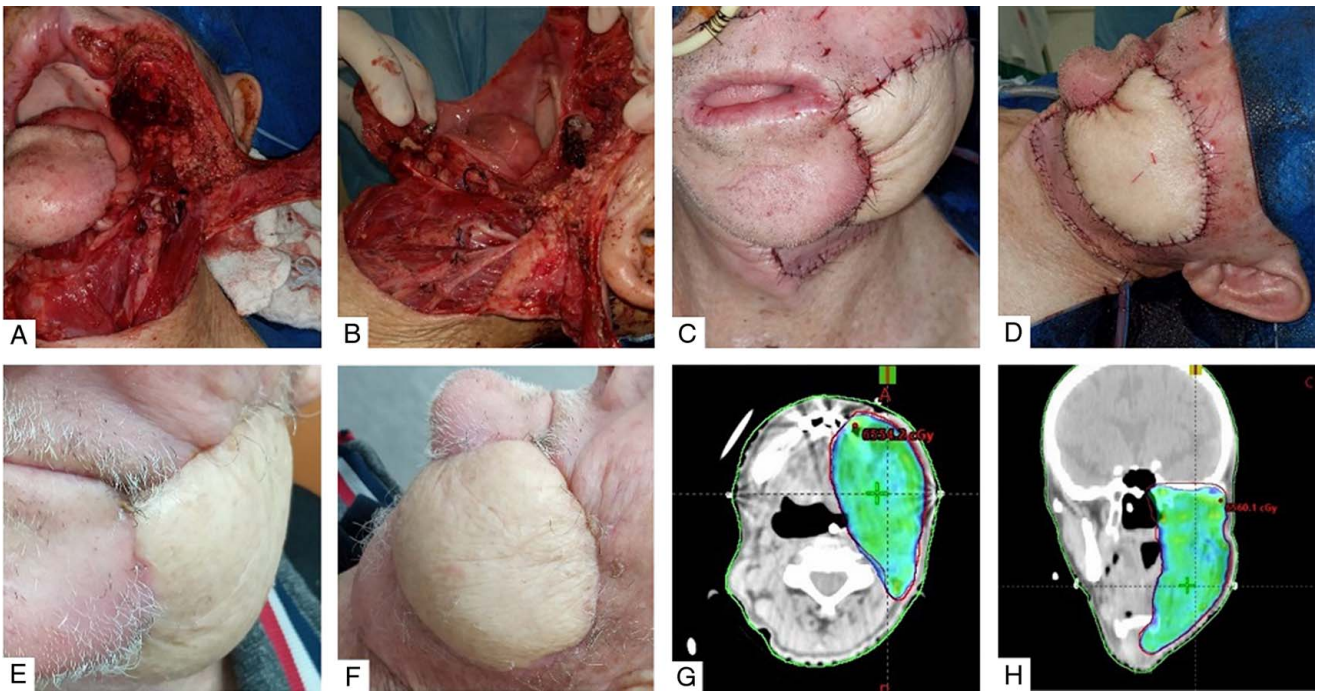

Figure 5. Multimodal therapy performed. (A–D) Show the segmental mandibulectomy and microsurgical reconstruction were performed using anterolateral thigh free flap. (E, F) Show 2 months of follow-up, and the ninth radiotherapy session. (G, H) Show the dose distribution between 6000 and 6681.6cGy in the axial and coronal slices, respectively.

advanced and non-surgical candidates can be treated with radical RT either combined or not with chemotherapy[16]. In the last few years, there has been an increase in the association of chemotherapy and radiotherapy (chemoradiation) with cytoreductive and potentiating purposes of their effects.

Most clinical failures occur during the first 2 years, knowing that the risk of developing a second primary tumour and/or tumour recurrence occurs in 20–30% of patients, basically in the upper aero-digestive tract[17,18].

Histologically, OSCC tends to be well or moderately differentiated, characterized by cells with higher and eosinophilic cytoplasm, round nuclei with mild hyperchromasia and desmosomes, areas of dyskeratosis and horny pearls have been observed. Whereas poorly differentiated OSCCs that occur less frequently, exhibit greater cellular atypia and loss of squamous characteristics, therefore, immunohistochemical analysis must sometimes be performed for confirmation of their diagnosis[19,20],

The degree of differentiation per *se* does not have a direct correlation with its prognosis, so that a combination of other histological risk factors such as tumour infiltration depth greater than 4 mm, perineural or lymph vascular invasion, bone infiltration and aggressive infiltration patterns are used[21]. Classification by the worst infiltration pattern according to those described in the literature are patterns from 1 to 5, and patterns 4 (isolated cells or groups of less than 15 cells) and 5 (satellite nodules with a distance greater than 1 mm from the neoplasm) have the poorest prognosis[21].

Among histological subtypes of OSCC, VOC is characterized by exophytic growth with an expansive invasive forehead and

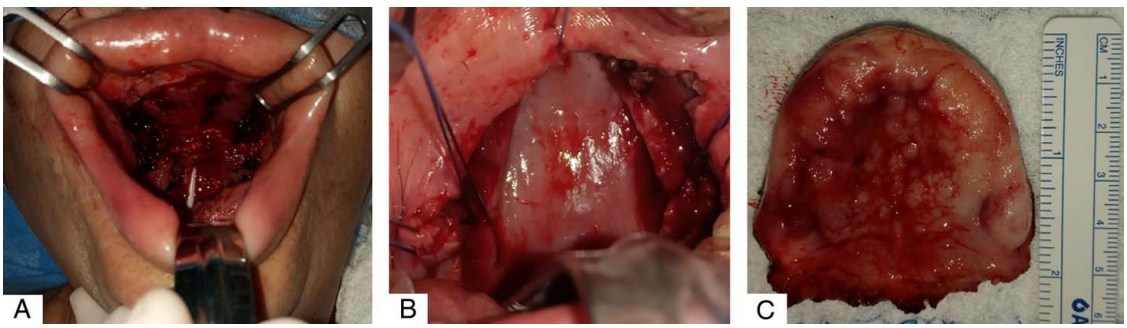

Figure 6. Surgery of oral squamous cell carcinoma in the hard palate. (A) Shows the tumour bed after total maxillectomy extending to the soft palate. (B) Shows the repair stitches with surgical bed traction. In (C) the surgical specimen is observed after tumour removal.

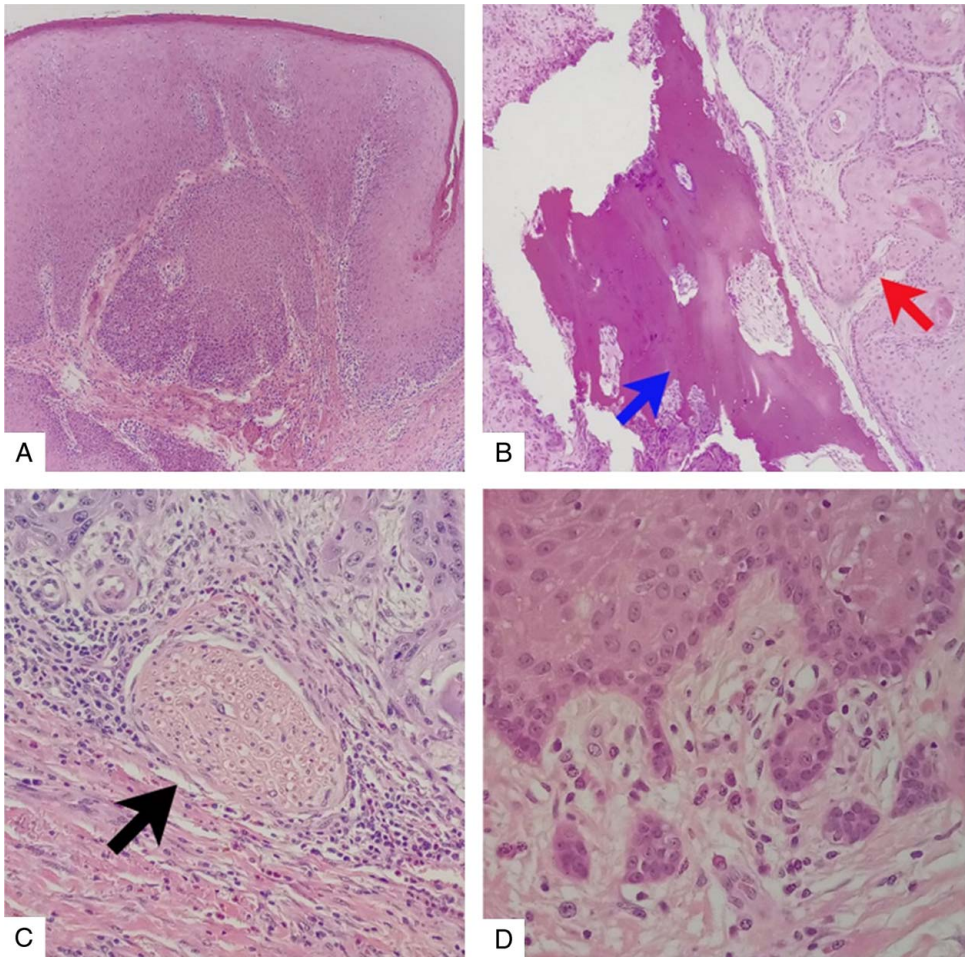

Figure 7. Histopathological analysis with hematoxylin and eosin (HE). (A) Case 1 (HE, × 40); Well-differentiated squamous cell carcinoma with minimal cellular atypia and broad invasive forehead featuring the verrucous subtype. (B) Case 2 (HE, × 100); Well-differentiated squamous cell carcinoma in an area of bone infiltration close to the anterior margin. Note the remnant of bone tissue (blue arrow) in the middle of the neoplasm (red arrow). (C) Case 3 (HE, × 100); Moderately differentiated squamous cell carcinoma in an area of perineural invasion. Note the nerve (arrow) in the middle of the desmoplastic stroma. (D) Case 4 (HE, × 100); Well-differentiated squamous cell carcinoma with a type 4 invasion pattern (isolated cells or clusters of < 15 cells in the tumour periphery).

minimal cellular atypia considered with better prognosis and non-metastatic dissemination (although it may progress to or coexist with a conventional SCC)[19].

Gingival carcinoma, irrespective of the histological type, in both maxillary bones have similar behaviours, the most frequent histological type being OSCC. Lymphatic drainage from this anatomical area includes levels Ib and II (submandibular and jugular-digastric region). Approximately 30% of patients show compromised lymph nodes during extraoral examination in cases of OSCC in mandibular gingiva. In the case of the maxillary gums, the rate of their involvement is between 13 and 24%. Local surgical resection with flap rotation seems to be the best option for treatment in the early stages of tumours in the mandibular gingiva, due to the low tolerance of the mandible to high doses of irradiation. Whereas, superficial lesions of the maxillary gingiva could involve the hard or soft palate and can be treated with RT exclusively, which reduces the extensive tissue removal caused by radical surgery. However, locally advanced lesions with bone cortical destruction and with positive lymph nodes should be treated with the combination of surgery and postoperative adjuvant RT[16,17].

Reconstructive surgery of the HNC is a well-established field in many cancer centres, however, the training and experience for performing extensive resections that could result in full-thickness tissue defects should be considered. Thus, if patients are submitted to inadequate treatments, this could lead to damage to oncological and functional outcomes in terms of quality of life. Among the most frequently described types of free flaps used to repair defects in the oral cavity, a recent study showed those: the ALT (82.7%), the radial forearm flap (9.1%), the scapula flap (9.1%), the fibula flap (6.1%) and the latissimus dorsi flap muscle (3%)[22]. Extensive tumour resections including full-thickness flaps are feasible, and reconstructive surgery becomes the best choice for restoring function and aesthetics and could be associated with higher rates of local control. The ALT is the most frequent alternative for the reconstruction of extensive defects, given its volume, good pedicle length and low morbidity of the donor area. In addition, the necessity for larger flaps for full-thickness defects might increase risk of flap failure[22].

Although primary chemoradiation is a relevant option for some patients with locally advanced disease, factors such as tumour location, previous adjuvant therapy in cases of multiple

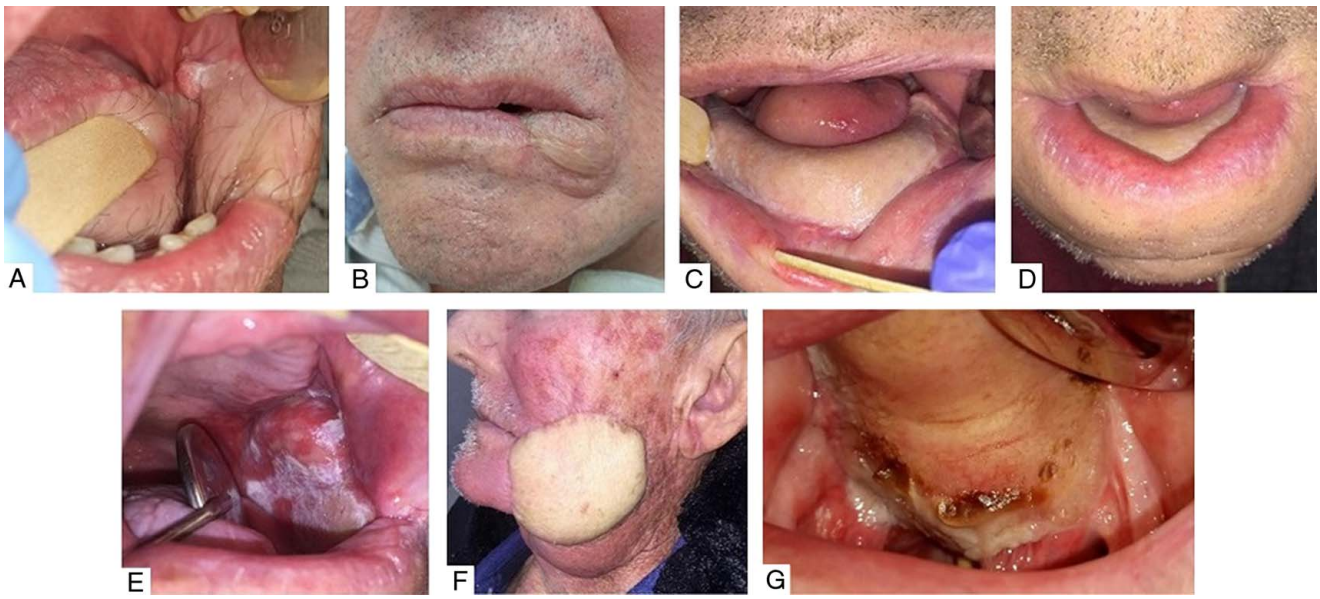

Figure 8. Three months of follow-up . (A, B) Case 1; Intra and extraoral examination that shows good clinical appearance of the flap in both locations, respectively. (C, D) Case 2: Intra and extraoral flap examination without signs of inflammation or clinical flap failure after radiotherapy (RT). (E, F) Case 3: Areas of oral mucositis surrounding the flap region were observed after the final session of RT and radiation-induced dermatitis grade 1 was shown in the extraoral region. (G) Case 4: Intraoral flap positioned in the hard palate, extending to soft palate with healing process.

relapses, medical records or factors associated with patients and treatment itself, radical surgery has been described as the best alternative for this primary approach. Preoperative RT is associated with an increased risk of free flap failure and further local side effects. However, in a recent study[23] that included 19 patients who undergone preoperative RT, a flap survival rate of 100% was observed. Flap failure is usually caused by vascular thrombosis caused by vasospasm and subsequent hypothermia, hypotension, and mechanical stress during microsurgical anastomosis. The risk of thrombosis increases by 80% on the second postoperative day and decreases by 10% after 3 days postoperatively. Otherwise, the microvascular free tissue transfer could also be successfully performed in patients who have undergone RT.

Postoperative RT (PORT) also has a wide range of consequences in the targeted tissue, including microvascular free flaps and implants placed in reconstructed areas. Acute and late radiation-induced side effects can jeopardize the succeed of both free flaps and implants for anchorage of oral rehabilitation. In one study, PORT increased the risk of ORN of microvascular bone flaps in 21-fold with the only predictor factor of greater than 60Gy RT[24]. An international consensus for PORT in H&N SCC (ORN) state that RT should be avoid in volumetric planification of the osseous component of the free flap[25]. Also, volumetric changes of flaps dampers almost 40% of its original volume and may be a challenge for surgeons to estimate the size to be harvest[26]. Other acute and late side effects such as mucositis, dysphagia, dermatitis, fibrosis, oesophageal stenosis, and swallowing disorders increase in appearance due to augmented tissue volume needed to be targeted in these cases[27]. Dental implants fail more in irradiated patients in time because of soft and hard tissue cumulative damage[28].

In this case series we showed a case of microsurgical reconstruction after resection of OSCC in the maxilla that involved hard and soft palate. In cases of extensive tissue defects or those located in anterior regions that make the use of maxillary obturators unfeasible, microsurgical free flaps are indicated[9,10]. Thus, different types of flaps have been used to repair these maxillary defects, with a success rate of ~ 95%. However, with regard to disadvantages, the need for long surgical times and recovery are outstanding, with potential risks for complications have been described[11], when compared with prosthetic filling. Furthermore, delays in the diagnosis of local relapses have been associated with the use of these flaps, although this continues to be controversial[10]. Whereas, the use of palatal obturators has been advocated for the reconstruction of small and medium-sized defects, the main advantages could be the short surgical time and hospital stay involved, and complete visualization of the tumour bed after total maxillectomy, which is helpful for the long-term follow-up. However, several disadvantages have been described, such as increased hypernasal speech, sinonasal-oral communication, difficulties with performing prosthetic hygiene and multiple prosthetic adjustments required that increase the number of tasks to deal with. Most studies have compared the two therapies based on the functional results obtained from use of prosthetic obturators and microsurgical flaps as the best choice for reconstruction. However, no significant differences were found between the two alternatives, therefore, the best option could be established by assessing the extension of reconstruction[11].

Conclusion

Microsurgical reconstruction with different types of flaps is a feasible and reliable therapeutic option for use after extensive surgeries caused by OSCC. RT has shown improvement in local control rates and has not been associated with flap failure in this case series. An adequate long-term follow-up to assess OS, DFS rates and quality of life must be carried out; however, cohort

studies would be necessary for better understanding of the role of each treatment in the multimodal scheme.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The number protocol for ethical approval was 4.930.402 / RC101/21 by our Institutional Committee of A.C. Camargo Cancer Center, Sao Paulo, Brazil.

Consent

Written informed consent was obtained from the full patients for publication of this case series and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

Conceptualization, W.E.B.-P.; Data curation, W.E.B.-P., M.L.R., H.P.C., F.S.B., M.C.C.; Formal analysis, W.E.B.-P.; Funding acquisition, W.E.B.-P.; Investigation, W.E.B.-P.; Methodology, W.E.B.-P., M.L.R., H.P.C., F.S.B., M.C.C., F.D.C. and A.C.A.P.; Resources, W.E.B.-P., K.A.V.-R., J.A.M.-Z. and A.C.A.P; Validation, W.E.B.-P., M.L.R., H.P.C., F.S.B., M.C.C., F.D.C., K.A.V.-R, J.A.M.-Z. and A.C.A.P.; Writing—original draft, W.E.B.-P.; Writing—review and editing, W.E.B.-P., M.L.R., H.P.C., F.S.B., M.C.C., F.D.C., K.A.V.-R., J.A.M.-Z., and A.C.A.P. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest disclosure

There are no conflicts of interest to declare in relation to this article.

Research registration unique identifying number (UIN)

Not applicable (Case series).

Guarantor

The guarantor of this case series is the corresponding author Wilber Edison Bernaola- Paredes who accept the full responsibility for the work and/or the conduct of this study, had access to the data, and controlled the decision to publish.

Data availability statement

Not applicable.

Provenance and peer review

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