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Prevention and treatment of microstomia

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The mouth, located in the lower third of the face, is a uniquely visible structure. It serves as a vital organ both aesthetically and functionally, playing a key role in speech, expression, and fundamental oral functions. Consequently, any alterations or defects in its shape, due to various causes, can lead to aesthetic and functional deficiencies. These issues may also result in challenges with social interactions and a decrease in confidence. In cases of microstomia, various surgical approaches are proposed based on the location, extent, shape, and cause of the defect, leading to numerous case reports. Plastic surgeons are proficient in oral reconstruction; however, cases of microstomia are relatively rare, which reduces their familiarity and interest in these cases. Additionally, preferences for oral size and shape vary according to factors such as geographical region and ethnicity, further complicating the functional definition of microstomia. Therefore, both subjective patient and physician judgments play crucial roles in the diagnosis and treatment of microstomia, as these may vary depending on individual and societal aspects. This review aims to classify the various causes and definitions of microstomia, as well as its non-surgical and surgical treatment options, with the goal of the treatment of this condition.

Abbreviations: ADM, acellular dermal matrix; PBSC, postburn scar contracture

Keywords: Lip / Microstomia / Mouth mucosa / Surgical flap

Review Article

INTRODUCTION

The mouth, a distinct structure in the lower third of the face, is a unique mobile organ that serves both cosmetic and functional purposes [1-4]. Although it typically maintains a specific anatomical position and size, preferences for the size of the mouth vary according to individual, racial, and societal factors, resulting in an ambiguous definition of microstomia [3,5,6]. As a result, subjective judgment significantly influences the diagnosis of microstomia. Alterations in the shape of the mouth or the presence of defects can cause issues with eating, drinking, speaking, expressing emotions, facial appearance, social interactions, and self-confidence [3,7,8].

Microstomia can result from congenital or acquired causes. Congenital microstomia typically arises in association with various syndromes, whereas acquired microstomia can develop following burns, trauma, connective tissue disorders, other diseases, or as a consequence of treatments for lip or oral skin cancer [5,9-11]. It is crucial to use appropriate reconstruction methods for defects caused by cancer or trauma to reduce the incidence of microstomia. This underscores the significance of proper reconstruction techniques and rehabilitation therapy in preventing this condition. Various reconstruction methods have been well-documented, taking into account the extent, location, and size of the oral defects, and research continues to explore other effective techniques [5,6,12-14].

Development of temporary microstomia is frequently seen after reconstructive surgery for oral cancer or trauma, which improves over time as scar maturation takes place or after non-

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surgical scar management. If microstomia persists without improvement, surgical intervention may be required. However, because microstomia often responds well to non-surgical treatments and is relatively rare due to its subjective diagnosis, plastic reconstructive surgeons may not be very familiar with it.

In this paper, we aim to review the definition of microstomia, its various causes, and both non-surgical and surgical treatments. Specifically, we intend to examine different reconstructive techniques for treating microstomia, with a focus on the oral commissure. This complex area is where the mucosa and orbicularis oris muscles of the upper and lower lips converge [1-4]. Reconstruction in this region presents challenges from both functional and aesthetic perspectives [15-17].

METHODS

A literature review was conducted on microstomia reconstruction and commissuroplasty for cases involving congenital factors, trauma, chemical and thermal burns, connective tissue diseases, and postoperative scenarios following lip cancer surgery. This review focused on studies published between January 1990 and July 2023 that were indexed in the PubMed database. Search queries utilized a combination of terms including "lip cancer," "microstomia," "mouth reconstruction," "lip reconstruction," "peri-oral defect," "oral defect," "commissuroplasty," "small mouth," "oral aperture," and "restricted oral or mouth." The inclusion criteria specified studies involving human subjects, published in English, addressing lip cancer reconstruction, conservative treatments, use of dental prosthetics, and reconstructions using skin grafts, local flaps, distant flaps, and free flaps in clinical settings. Exclusions were made for animal studies and publications not in English. Additionally, supplemental hand searches were conducted on the bibliographies of relevant papers and extensive searches for "related articles."

RESULTS

The search query identified 250 publications, of which 124 articles were available in full-text form. Thirty studies were excluded after a review of the title and abstract. The complete texts of the remaining 94 articles were reviewed to determine suitability for inclusion. This led to the exclusion of 21 articles. A review of the references in the remaining eight articles yielded 18 more studies to be included, for a total of 91 studies. Among these, there were eight books, 21 case reports, 55 original articles, and seven review articles. Papers addressing a range of topics, including causes, non-surgical treatment, surgical treatment, and commissuroplasty, were frequently classified into multiple categories. This overlap occurred because the descriptions within the papers were often intertwined, complicating the assignment to a single category.

ANATOMY OF THE MOUTH

The mouth consists of three layers: mucosa, orbicularis oris muscle, and skin. It has a distinctive anatomical structure, marked by a groove-shaped depression at the center of the upper lip, known as the philtrum. Below the philtrum is a V-shaped feature called the Cupid's bow. The edges of the lips are outlined by the white roll, and damage in this area often leads to noticeable scarring, highlighting its significance as an anatomical landmark. The muscles of the mouth, primarily the orbicularis oris, encircle the mouth and converge at the lip ends to form the modiolus, which enables the function of the oral sphincter [1-4].

DEFINITION AND DIAGNOSIS OF MICROSTOMIA

Given that the mouth serves both functional and aesthetic purposes, it is logical to categorize microstomia in terms of functional and aesthetic aspects. From a functional standpoint, the diagnosis of microstomia is based on subjective criteria, which include assessing difficulties in eating and the ability to insert a teaspoon into the mouth without issues, as well as maintaining oral hygiene (Table 1) [5].

Objective criteria are crucial for the accurate diagnosis of microstomia. In terms of mouth opening, the average vertical mouth opening is generally considered to be 40–50 mm. Functional opening ranges from 25 to 35 mm, while a limited opening is defined as being between 10 and 24 mm [18-20]. Other criteria for measuring microstomia involve determining the

Table 1. Criteria for microstomia assessment

	Criteria	
	Subjective	Objective
Normal	1. No eating problems 2. Can put a teaspoon in the mouth 3. Satisfactory oral hygiene	Both commissures at the level of the medial limb
Moderate	1. No eating problems 2. Can put a teaspoon in the mouth 3. Satisfactory oral hygiene	One commissure or both at or lateral to the alar facial groove but medial to the medial limb
Severe	1. Eating problems 2. Cannot put a teaspoon in the mouth 3. Poor oral hygiene	One commissure or both medial to alar facial groove

Adapted from Shaikh et al. GMS Interdiscip Plast Reconstr Surg DGPW 2022;11: Doc02 [6].

positions of both the commissure and the medial limb of the eye relative to their normal locations. Microstomia is diagnosed if the mouth corner is positioned inside the medial limb of the eye. Some assessments use the midpupil as a reference point instead of the medial limb of the eye [2,21]. Additionally, interincisal distance and intercommissural distance are meaningful measurements, although clear standards are lacking due to variations in individual body characteristics and racial differences [5,6,21]. From an aesthetic standpoint, the perception of microstomia varies based on racial, national, and social factors, as well as the patient's self-image. Consequently, no specific criteria are provided.

When diagnosing microstomia, it is desirable to consider objective criteria and functional measurements, as well as subjective assessments of severity by both patients and physicians. Additionally, the patient's self-image, along with societal, temporal, and racial factors, should be taken into account.

CAUSES OF MICROSTOMIA

Subjective aesthetic purposes are not considered a cause of microstomia in this paper. The causes of microstomia include congenital and genetic disorders, burns (thermal, electric, chemical), post-facial trauma, microstomia associated with connective tissue disorders, following reconstruction of lip cancer, and others. Notably, microstomia often occurs after surgical treatment for lip and oral cancer [5,11].

Congenital causes

Microstomia is associated with several conditions, such as cleft lip and palate, micrognathia, and craniocarpotarsal dysplasia, including genetic disorders such as partial duplication of chromosome 6q, Hallopeau–Siemens-type recessive dystrophic epidermolysis bullosa, Freeman–Sheldon (whistling face) syndrome, Burton skeletal dysplasia, Plummer-Vinson syndrome, Goltz syndrome, and others [22-24].

Connective tissue disorders

Microstomia occurs in individuals with conditions such as systemic sclerosis, scleroderma, systemic lupus erythematosus, scleromyxedema, restrictive dermopathy, and dystrophic epidermolysis bullosa, among others. It typically develops after chronic mucosal inflammation, which results in scarring of the buccal and labial mucosa as well as the commissures [25-28].

Trauma

Trauma-induced microstomia primarily occurs through thermal, chemical, and electric burns, often manifesting together with severe injuries. Thermal burns lead to post-burn scar contractures. Perioral facial burns are particularly prone to scar contractures due to the curved nature of the skin, mucosa, and orbicularis oris muscle [7,29]. The severity of contractures can vary depending on the depth of the burn and the extent of skin and muscle involvement, which in turn affects the clinical symptoms, treatment methods, and surgical complexities. In cases of chemical burns, particularly those resulting from suicide attempts using caustic substances, the injuries predominantly affect the intraoral mucosa. This often leads to trismus due to scar contracture, which can result in microstomia. The causative agent results in liquefaction necrosis by bonding with tissue proteins. This injury leads to scarring of the buccal mucosa, leading to microstomia and ankyloglossia [30-32]. Additionally, trauma-induced microstomia can occur due to traffic accidents, bite injuries (from animals or humans), and lip tissue defects caused by gunshot injuries.

Surgical treatment of lip and oral cancer

Temporary microstomia occurs immediately following tumor ablation surgery in many cases. However, the symptoms of microstomia often subside after the scar matures over a period of 6 to 12 months. When reconstructing lip cancer with a small tumor size using methods such as simple wedge excision, W-excision, or step ladder excision, the occurrence of permanent microstomia is rare. In cases involving large tumor sizes, extensive intraoral mucosa involvement, and reconstruction techniques like the Estlander flap reconstruction or Webster flap reconstruction, permanent microstomia is more common [5,33-36]. Therefore, after reconstructing large defects using techniques such as Gilles Fan reconstruction, Karapandzic flap reconstruction, and Fujimori gate flap reconstruction, there is a higher incidence of microstomia [36,37]. However, many patients may not perceive themselves as having microstomia if they adapt well to activities like eating and maintaining oral hygiene on a subjective level, and thus may not actively seek treatment. Conversely, some patients may lead relatively normal lives but struggle with tasks such as opening their mouths wide enough for dental procedures or other treatments, which prompts them to seek therapy [38].

Other causes

Microstomia is related to toxic epidermal necrosis and Steven-Johnson syndrome [39,40]. Other rare causes include congenital maxilla-facial syngnathia and synechiae involving the tongue and lip [31,40].

SYMPTOMS OF MICROSTOMIA

Functional difficulties in eating, poor intraoral hygiene, and pronunciation issues often occur. Poor oral intake and impaired dental hygiene can lead to malnutrition, severe tooth decay, halitosis, and recurrent oral infections, which are challenging to treat due to limited access. Additionally, issues with facial expression, self-esteem, and social interaction are commonly observed. While some individuals may not experience functional issues, they often seek dental treatment to improve their ability to open their mouths. If there are ongoing limitations in dental treatment, active treatment for microstomia may be necessary [39]. There are instances where patients request mouth enlargement for subjective cosmetic reasons. In such cases, it is important for the surgeon to take time to thoroughly understand the case through detailed consultations with the patient and to actively grasp the patient's intentions. Sometimes, it is also necessary to actively persuade patients that their condition is normal.

SELECTION OF AN APPROPRIATE RECONSTRUCTION METHOD TO PREVENT MICROSTOMIA

Microstomia frequently occurs after surgery for oral cancer reconstruction. Consequently, employing appropriate lip cancer reconstruction methods and conservative treatments can help reduce the incidence of microstomia. There are over 200 known methods for reconstructing total or near-total lower lip defects. However, most authors do not discuss the occurrence of microstomia following reconstruction surgery, resulting in limited research on the risk of microstomia associated with each method. Some authors have noted a decrease in the frequency of microstomia by using their specific reconstruction techniques. These authors have observed a reduced incidence of microstomia in cases of near-total or total reconstruction using techniques such as the bilateral Yu flap, bilateral Mutaf flap, and composite radial forearm free flap, and have developed algorithms for these procedures [5,37,41-47]. They also report a low incidence of microstomia in their case studies.

The incidence of microstomia differs markedly between reconstructions for small and large skin cancers. Moreover, it is believed that various factors, including the patient's level of adaptation, surgical trauma, the surgical technique employed, scar maturation, and the choice of an appropriate reconstruction method, influence the occurrence of microstomia [5,37].

TREATMENT OF MICROSTOMIA

Purpose

The lips of the mouth play crucial roles in functions such as speech, expression, basic oral tasks, social interaction, and self-esteem. The reconstruction of the lip and treatment of microstomia focus on restoring these capabilities. This includes recreating the oral sphincter, repositioning the lower lip, and improving both function and aesthetics to help individuals reintegrate into society [1-4,48,49].

Treatment methods

When discussing reconstruction of the lip and oral commissure–a complex three-dimensional anatomic region that merges skin, mucosa, and muscle–it is crucial to remember that the esthetic and functional aspects of the lip are strongly interconnected and cannot be considered separately from each other [17].

Non-operative methods

After experiencing trauma (such as burns or accidents) or undergoing surgical treatment for carcinoma, it is common to wait approximately 6–12 months for scar maturation and improvement in microstomia. During this waiting period, employing techniques like massage, dental impressions, and prosthetic rehabilitation is recommended to aid symptom improvement. Most cases tend to improve with conservative treatment. However, if symptoms of microstomia continue beyond this period, active surgical intervention may be considered.

1. Observation

Appropriate interventions for microstomia include mouth opening training, exercises, prosthetics, and serial expansion using dental impressions. These should be continued over a period of 6-12 months to allow scar maturation. During this time, significant improvements in microstomia are often observed.

2. Hyaluronidase injection and botulinum toxin

Reports suggest that hyaluronidase contributes to the prevention and treatment of microstomia in systemic sclerosis or mixed connective tissue disease by hydrolyzing glucosaminidic and glycosidic bonds in hyaluronic acid and other connective tissue mucopolysaccharides [50,51]. Furthermore, improvements in microstomia have been observed in scleroderma patients treated with onabotulinumtoxin A, suggesting that multiple treatment approaches are available [52].

3. Prosthetic rehabilitation

After the occurrence of microstomia due to various causes such

as trauma, cancer ablation surgery, or burns, patients may be treated by either reusing their existing dentures or creating new ones using different types of dental impression trays, which include both conventional and digital methods applied serially [1,2,20,53]. There are studies that categorize oral appliances based on their shape, direction, and position. These appliances are classified by stretching direction as horizontal, vertical, or circumoral, and by the position of the appliance as either intraoral or extraoral. The literature introduces various types of oral appliances and summarizes their advantages and disadvantages. Factors to consider when selecting the appropriate appliance include the suitability for children, the feasibility of wearing the appliance for extended periods, the ease of removal for eating or social activities, the effectiveness of the appliance in treating microstomia based on the stretching direction, and the necessity of teeth for attachment. In conclusion, it is suggested that the incidence of microstomia decreases and the need for surgical intervention is reduced with the proper application and maintenance of these appliances [38,54,55]. Additionally, for other conditions such as systemic lupus erythematosus and connective tissue diseases, educational oral care programs are introduced to prevent microstomia resulting from mucosal and skin inflammation. Furthermore, various methods for preventing microstomia, including the use of microstomia prevention tubes and one-piece static serial orthoses for gradual mouth opening, have also been developed [56-59].

Operative methods

There are numerous methods for lip reconstruction, and selecting the right one based on the cause, location, and size of the defect is crucial. To date, more than 200 reconstruction techniques involving various donor sites have been introduced, making it essential to choose the most suitable method for each individual case [21,32,40,46,47,60-73].

The surgical technique for microstomia was first described by Dieffenbach in 1831, who used a Y-V advancement of superior, inferior, and lateral mucosal flaps following a wedge-shaped excision of the scar. Subsequent modifications to the method were introduced by Converse, Friedlander, and others. Since then, various methods have been researched [71,72,74].

1. Operative treatment of microstomia

Depending on the severity of microstomia, treatment options in mild cases include simple scar excision, scar excision with a split-thickness skin graft, or a full-thickness skin graft. Scar release can also be performed using local flaps such as V-Y, Y-V, rhomboid flap, multiple Z-plasty, or distant flaps. The choice of treatment depends on the extent of tissue involvement, including skin, mucosa, and muscle. In severe cases of microstomia, where surrounding tissue is unavailable, correction may be achieved using distant flaps or free flaps [20,29,40,74-76]. Microstomia resulting from burns can be corrected through various surgical techniques, including triangular excision at the mouth corner, V-Y or Y-V advancement flap, scar revision, and wound closure using either full-thickness or split-thickness skin grafts, or two rhomboid flaps. Studies have shown that mucosal advancement flaps yield better outcomes than scar revisions or skin grafts [77,78]. Overcorrecting by 2–4 mm and employing splints after surgery are effective strategies to prevent the recurrence of contracture and microstomia [79].

2. Reconstruction of the oral commissure

Reconstruction of the oral commissure is an essential aspect of surgical treatment for microstomia, as it involves enlarging the mouth's overall size. Tissue defects at the oral commissure present significant challenges in reconstruction, often leading to abnormalities in the shape of the mouth corner and the development of microstomia after reconstruction, which results in both functional and aesthetic issues [20]. Choosing an appropriate method for reconstructing large mouth corner defects is particularly challenging. The Estlander flap has been the most commonly used method for reconstructing wide mouth corners. However, some authors have reported numerous cases of microstomia following Estlander flap procedures, highlighting the need for more effective reconstruction methods for mouth corner defects [5,42,43].

One notable method is commissuroplasty using the Zisser flap, which has been reported to reduce microstomia in 13 cases involving tumor excision, trauma, burns, and other conditions [17]. The author modified this technique into the Hatchet flap for mouth corner reconstruction, effectively reducing the risk of microstomia [80].

Since the oral commissure involves the merging of skin, mucosa, and sphincter muscle, split or full-thickness skin grafts are not recommended due to the risk of secondary contracture. Instead, reconstruction methods using local flaps such as the V-Y, Y-V flap, multiple Z-plasty, and rhomboidal flap are advised [38,63,71,72,81-84]. Additionally, various local flaps, distant flaps, and free flaps are introduced as alternative reconstruction options [4-6,74-76].

Kazanjian and Roopenian [82] presented two methods of reconstruction that were both functionally satisfactory and aesthetically acceptable. Karapandzic [36] employed local arterial flaps for the reconstruction of lip defects. Berlet et al. [81] suggested the necessity of flap reconstruction at the oral commissure for treatment and prevention purposes due to reduction in oral aperture

caused by scars after skin grafting or oral surgery for burns. They performed commissuroplasty using a nasolabial flap with tugging and fixation. They also argued that flap reconstruction may be necessary when oral splint placement is difficult due to patient cooperation issues (this approach would be better suited for middle-aged or older patients with a certain degree of a distinct nasolabial fold). Sari et al. [16] reported successful results using the asterisk design to create the commissure and, if necessary, simultaneous use of the Abbe flap. Ayhan et al. [7] separated the auricular lobule graft from the postburn scar contracture (PBSC) commissure in a V-shaped configuration, creating a composite graft for commissure reconstruction. They noted that the color and shape of the commissure were well-matched and that this technique was suitable for deep tissue burns. Osaki et al. [85] used a modified Z-plasty technique in cases of split dry lip for commissure reconstruction. Wood et al. [8] discussed the application of acellular dermal matrix (ADM) in buccal reconstruction for treating microstomia resulting from recurrent infection. They contended that ADM surpasses skin grafts in effectiveness because it reduces inflammation, fibrosis, and keratinization [8,25,26]. Additionally, ADM eliminates donor site morbidity and furnishes a matrix composed of collagens, elastin, vascular channels, and proteins, which facilitate revascularization, cell repopulation, and tissue remodeling.

Dang et al. [86] introduced commissuroplasty with a triangular cheek flap, utilizing tissue from a free flap previously used for mouth reconstruction. Grishkevich [32] recommended that in cases of PBSC microstomia, the edge of the mouth orifice should be managed with V-Y-shaped incisions and trapezoidal designs rather than skin grafts. Monteiro et al. [87] performed commissuroplasty using a fish-tail flap at the mouth corner, successfully restoring the unique architecture of the oral commissure and increasing the intercommissural distance by more than 10 mm and the interincisal width by more than 5 mm. This resulted in both functional and aesthetic improvements. The author utilizes a modified Converse technique along with this fish-tail flap method, regarding it as an easy, safe, and reliable approach for independent reconstruction of the mouth corner (Figs. 1, 2).

Microstomia resulting from thermal burns and chemical burns exhibits differences in location and histological characteristics. In instances of facial burns, it primarily affects the exposed areas, specifically the skin surface at the commissure. Conversely, chemical burns mainly affect the mucosa, even when the skin remains intact [30]. The author's previous report and Chidzonga

Fig. 1. Microstomia caused by chemical burn with caustic soda in a 65-year-old woman demonstrating the author's preferred commissuroplasty method. (A) Preoperative photograph. (B) Design for excision of a double triangle (a': mouth corner on skin, b': mouth corner on mucosa, a: new mouth corner on skin, b: new mouth corner on mucosa). (C) Immediately postoperative photograph. (D) Photograph 1 year after the operation.

categorized the correction of microstomia resulting from caustic soda and PBSC microstomia based on location. Chemical burns are known to cause liquefaction necrosis of tissue proteins, which leads to trismus due to mucosal scarring, followed by ankyloglossia and microstomia (Fig. 3) [30,88].

In the correction of microstomia, flap reconstruction, particularly using local flaps, is generally recommended. However, when mucosal involvement necessitates skin grafting, such as in cases of acquired synechiae of the tongue to the floor of the mouth, focusing on surface reconstruction instead of reconstructing the mouth corner can be more effective [31,87,88]. Another important aspect of microstomia reconstruction is preserving the sphincter function and the integrity of the orbicularis oris muscle after reconstruction. During the removal and repair of scar tissue, it is essential to identify and repair healthy muscle through a technique known as rolling, which helps maintain the integrity of the orbicularis oris muscle. In instances of extensive defects at the mouth corner, Demir et al. [89] reported the use of split masseter transposition to preserve sphincter muscle function. Ayhan et al. [7] stated that a new modiolus was sutured and formed at 1 cm on the lateral side of the commissure. Branch and David [73] successfully corrected microstomia in a 10-week-old infant. They discussed the resolution of associated issues such as growth impairment and speech difficulties, which are often exacerbated by severe microstomia due to challenges in oral intake. To approach these problems, they employed multiple Z-plasty and rhomboi-

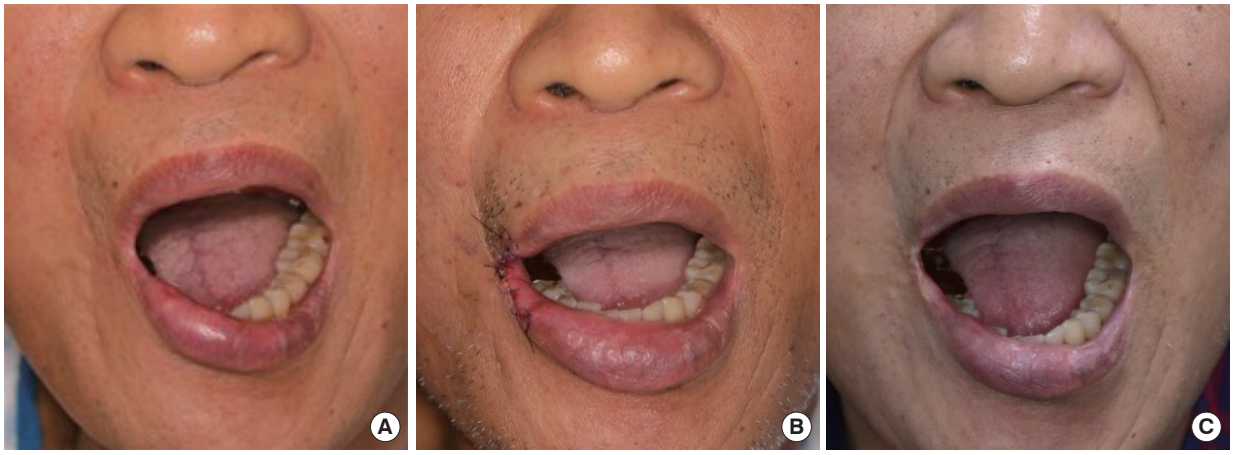

Fig. 2. Microstomia after reconstruction of a squamous cell carcinoma of the right mouth corner in a 69-year-old man. (A) Preoperative photograph. (B) Immediately after right commissuroplasty. (C) Six months after the reconstruction. Adapted from Ki Sh et al. J Craniofac Surg 2024;35:e359-61 [89].

Fig. 3. Microstomia caused by chemical burn (caustic soda) in a 54-year-old woman. (A) Microstomia caused by chemical burn: mucosal contracture without involvement of the skin. (B) Contracture release with full-thickness skin graft from the groin. (C) Two months after the reconstruction.

dal flap techniques, highlighting the importance of addressing microstomia even in infants.

Operation and dentures

It has been reported that excellent outcomes can be achieved by employing the various surgical treatment methods introduced earlier and by immediately placing dentures or prosthetics [53,90].

Distraction osteogenesis

Distraction osteogenesis is performed in cases of congenital malformations or microstomia resulting from growth disturbances of the jaw [91,92].

RESULTS AND COMPLICATIONS OF MICROSTOMIA TREATMENT

Due to the constant movement and contact with food, infections and disruptions of wounds in the oral cavity are common, necessitating meticulous care. Therefore, as previously mentioned, local flaps using healthy tissue are preferred over skin grafts for repairing these injuries. In most cases, it has been reported that following commissuroplasty, the interincisional distance and mouth opening increase by 10 mm or more. We suggested that severe microstomia, resulting from burns and commissuroplasty, can lead to oral incompetence. This condition may arise secondary to injuries or dysfunction of the orbicularis muscle, adhesions of the tongue or lips, or recurrent contracture. Furthermore, in cases involving repeated recurrence and scarring, there is a potential risk for the development of carcinoma [21].

CONCLUSION

Oral commissure reconstruction is a meticulous process that requires careful consideration of both aesthetic and functional aspects. Therefore, reconstructive surgeons must thoroughly understand the normal anatomy of the mouth corner and be familiar with the advantages and disadvantages of various reconstruction methods. The objective is to restore a normal appearance aesthetically and to enable eating and speaking functionally after surgery.

NOTES

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Patient consent

The photographs in Figs. 1-3 were provided by the author after obtaining informed consent from patients.

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