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The Development of the Parotid Salivary Gland: Determining Factors for Topographic and Vascular Complexity in the Maxillofacial Region

Desarrollo de la Glándula Salival Parótida: Factores Determinantes de la Complejidad Topográfica y Vascular en la Región Maxilofacial

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SUMMARY: The parotid salivary gland is a critical structure in the maxillofacial region that exhibits intricate anatomical relationships with neurovascular elements. These relationships are significantly shaped by embryonic development. This article summarizes current knowledge on the embryogenesis, anatomical organization, and clinical relevance of the parotid gland, emphasizing how developmental processes dictate its adult morphology. The parotid gland embryologically originates from the ectodermal oral epithelium at 8-9 weeks of gestation and undergoes branching morphogenesis, which is regulated by growth factors (FGF, TGF, and EGF), extracellular matrix components (collagen III/IV and fibronectin), and genetic mechanisms (e.g., microRNA-21). Apoptosis-driven lumen formation and myoepithelial cell differentiation refine ductal architecture further by mid-gestation. Postnatally, hypoxia and signaling pathways continue to influence maturation. Anatomically, the gland's lobular structure is divided into superficial and deep lobes by the facial nerve and exhibits variability in processes (e.g., temporal and facial) and ductal anatomy. The gland's close association with the facial nerve, external carotid artery, and parotid fascia highlights the complexity of surgery. Topographic variability, such as the presence of accessory glandular tissue (prevalent in 32-36 % of cases) and ductal branching patterns, impacts diagnostic and therapeutic precision. Clinical correlations underscore the importance of embryological knowledge in managing neoplasms, trauma, and iatrogenic nerve injuries. Understanding the developmental determinants of glandular architecture and neurovascular relationships improves procedural accuracy in maxillofacial surgery and reduces morbidity. This review emphasizes the interdependence of embryology, anatomy, and clinical practice, advocating for an integrated approach to managing parotid pathology.

KEY WORDS: Salivary Glands; Parotid Salivary Gland; Parotideomasseteric region; Development; Maxillofacial Surgery.

INTRODUCTION

The orofacial region is one of the most complexly organized areas of the human body. The vascularization, innervation, and features of the organs and musculoskeletal apparatus in this region remain important subjects of study for specialists to this day (Scianna & Petruzzelli, 2007; Thielker *et al*., 2018). The major salivary glands, especially the parotid glands, occupy a special place in this system. The anatomy of these glands varies significantly depending on various aspects of embryogenesis. Due to the complex organization of these structures, the pathology of this area is unique. According to the Russian Ministry of Health, salivary gland neoplasms account for 1-5 % of all malignant tumors and 3 % of head and neck tumors. The number of patients with maxillofacial pathology is increasing every year, requiring a more thorough study of the anatomy of these structures to successfully provide medical care to the population (Merabishvili *et al*., 2016; Kutukova *et al*., 2020).

Features of the embryonic development of the parotid salivary glands

During the third week of embryonic development, an oral fossa (also known as an oral bay or stomodeum)

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forms as a result of the indentation of the cutaneous ectoderm at the head end of the embryo's body. This structure later becomes the primitive oral cavity and forms the basis for different types of mucous membranes. Initially, the oral fossa and the anterior intestinal cavity are separated by the pharyngeal membrane, the stomodeum's floor. Later, the membrane breaks through with the formation of the initial digestive canal due to the fusion of these components (Patel *et al*., 2006; Chen *et al*., 2017). The question of the embryonic origin of the oral epithelium is still under discussion, but a significant number of studies in this area lean towards the ectodermal-skin theory (Espín-Ferra *et al*., 1991; Miletich, 2010; Soukup & Horácek, 2013; Holmberg & Hoffman, 2014; Sagai *et al*., 2017; desJardins-Park *et al*., 2021; Reimnazarova *et al*., 2021).

The connective tissue and smooth muscle components of these structures originate from ectomesenchyme, which forms when the paraxial and lateral sections of the mesoderm fuse with cells that migrate from the neural crest and ectodermal placodes. The epithelial component of the parotid salivary glands is derived from the ectodermal epithelium of the primary oral cavity, though the genesis of the sublingual and submandibular salivary glands is controversial due to their endodermal origin (Gasser, 1975; Patel & Hoffman, 2014; Myadelets, 2021). Several authors have noted signs indicating their endodermal nature. However, this remains unconfirmed due to the absence of endodermal markers, which could confirm this theory (Reimnazarova *et al*., 2021).

The formation of glandular structures is a complex, multi-step process involving the unification of various embryo tissues, blood vessels, nerves, and lymphatic structures. Salivary gland formation begins at six to seven weeks of embryonic development when the submandibular gland begins to form (Thiemann *et al*., 2022). The parotid and sublingual salivary glands form a little later, at eight to nine weeks of intrauterine development. Morphological criteria for the formation of parotid salivary glands appear at 11-12 weeks of embryogenesis when an epithelial process from the primitive oral mucosa of the embryo appears in the area corresponding to the parotideomasseteric region of an adult. Over time, there is active proliferation and differentiation of internal epithelial cells (controlled by increased signaling of various growth factors), which leads to significant enlargement and dichotomous branching into strands that give rise to future lobules of the gland. These processes result in a structure similar in shape to the future organ, but in the growth stage (Hauser & Hoffman, 2015; Suzuki *et al*., 2021; Aure *et al*., 2023; Ray & Soriano, 2023; Song *et al*., 2023).

The mesenchymal compartment of the structure serves as the rudiment of the future gland capsule and its connective tissue elements. It acts as a source of differentiation and proliferation factors, including fibroblast growth factor (FGF), transforming growth factor (TGF), and epidermal growth factor (EGF). Increased levels of heparan sulfate, a component of the amorphous matrix, correlate with more intensive proliferation of acinar precursor cells and branching of the gland (Harunaga *et al*., 2011; Li *et al*., 2024). The boundary between these two embryonic components is the extracellular matrix layer (basement membrane), which, over time, is replenished with synthesized components of the intercellular substance. This basement membrane is of fundamental importance in the attachment of the epithelium to connective tissue.

Many of these components are necessary for the normal development and subsequent functioning of the gland. Collagen, mainly of type 3, forms concentric layers around future ducts and contributes to the formation of clefts, which initiate branching of the gland. Type 4 collagen underlies the formation of basement membranes for the glandular epithelium (Katsuno-Kambe *et al*., 2021). Matrix metalloproteinases (MMP2 and MMP14), intercellular interaction proteins (integrins and cadherins), and several growth factors (including fibroblastic and epidermal) stimulate development (Katori *et al*., 2013; Teshima *et al*., 2016a,b; Guan *et al*., 2019; Goodwin & Nelson, 2020; Micucci *et al*., 2021). The proteins fibronectin and laminin (isoforms 511 and 512) also contribute significantly by participating in the initiation of branching and forming the basis of basement membranes, which are necessary for any structure with epithelial parenchyma (Miletich, 2010; Goodwin & Nelson, 2020). The role of SOX9 in regulating salivary gland organogenesis is currently under active study. According to D. Tanaka, eliminating SOX9 through enzyme systems during the early stages of salivary gland development leads to hypoplasia or aplasia of these glands. This demonstrates the crucial role SOX9 plays in their development. This finding is supported by a publication, which shows a strong correlation between the expression level of this factor and the regenerative capacity of salivary glands (Chatzeli *et al*., 2017).

Patel and Hoffman highlight the significance of posttranslational protein modifications in gland branching morphogenesis, a process in which glycosylation and microRNA (miRNA) pathways play a pivotal role. miRNAs are non-coding nucleotide sequences that can influence gene expression. One variety, miR-21, is activated by epidermal growth factor and regulates signaling pathways that affect fibroblastic growth factor-

dependent genes that regulate the synthesis of E-cadherin and heparan sulfate. This indirectly affects growth and development (Zigiotti *et al*., 1991; Patel *et al*., 2006; Touré & Vacher, 2010; Song *et al*., 2023). Decreased gene expression or synthesis of the aforementioned proteins, or the formation of autoantibodies to them, seriously affects the morphogenesis of parotid salivary glands. This leads to hypoplasia, disorganization of the epithelium, and disruption of organ structure formation (Touré & Vacher, 2010). Later in the formation of parotid gland structures, many outgrowths form at the ends of the cords in the form of epithelial kidneys. These kidneys give rise to the terminal sections and excretory ducts (Patel *et al*., 2006; Pinares-Toledo *et al*., 2018; Kumar *et al*., 2020). The duct lumen appears at three months of embryonic development by initiating proapoptotic mechanisms that lead to the death of epitheliocytes in the center of the processes and release the space they occupied (Shibuya *et al*., 2016; Urkasemsin & Ferreira, 2019). M. Sakai states that the mTOR signaling pathway plays a significant role in the branching and development of the salivary gland duct system. The researchers demonstrated decreased duct branching and acinar cell hypoplasia when using rapamycin, an inhibitor of the mTOR pathway, in an ex vivo experiment.

According to some reports, such processes are preceded by the appearance of apicobasal cell polarization, which leads to a number of biochemical transformations. However, this theory is currently under discussion (Myadelets, 2021). There is also a theory about the initial genetic determination of centrogenic cell death, as by the third month, they no longer express genes characteristic of peripheral embryo cells and do not secrete proteins characteristic of future acinar structures (Chibly *et al*., 2022). Meanwhile, the differentiation of secretory cells begins. These cells have a number of features and differences depending on the structure and type of secretion of future exocrinocytes. According to this feature, there are three types of terminal sections: serous, mucous, and mixed. The parotid salivary gland, for example, is mainly composed of serous glands, which indicates the nature of its secretion. Terminal differentiation processes do not end at the intrauterine stage but continue during postnatal development, which is associated with hypoxia in the first months after birth. Myoepithelial cells are also important for the functioning of the salivary glands. They are visually defined among the rudimentary terminal sections at the end of four months of intrauterine development. They originate from the outer layer of cuboid kidney cells of developing acinuses (Lee *et al*., 2024). In a functioning gland, they contract under the influence of cholinergic innervation and stimulate the release of primary saliva into the lumen of the acinuses (Ugˇur & Tercanli, 2024).

Understanding the embryogenesis of structures located near the parotid salivary glands is an important aspect of comprehending the features of embryonic development. These structures include the facial nerve, the external carotid artery, and the retromandibular vein. The extracranial portion of the facial nerve has complex anatomy, with numerous branches in various locations that can vary depending on the stage of embryonic development. In their article, Guizetti & Radlanski (1996) describe the relationship between the parotid salivary gland and adjacent structures during intrauterine development. They note that, in early stages, the facial nerve lies laterally and cranially to the parotid gland; neither the main trunk nor its branches pass through the gland's parenchyma. At this time, the external carotid artery and retromandibular vein are integrated into the glandular tissue and located in the distal parts of the gland. Later, due to an increase in the size of the organ and surrounding soft tissues, some facial nerve branches become surrounded by the gland's parenchyma, primarily the buccal and zygomatic branches. As the gland continues to develop, the main trunk of the facial nerve enters its parenchyma completely and branches into different groups. The external carotid artery and retromandibular vein remain in the distal portion of the gland (Guizetti & Radlanski, 1996).

The relationship between anatomy and topography

The combination of the aforementioned features of parotid salivary gland embryogenesis and the factors ensuring proper organ development during the prenatal period dictate the conditions for variability in its structure, even with minor changes in the influence of these stimuli on the developmental process. The parotid salivary gland is located in the parotideomasseteric (preauricular) region. Its average boundaries are considered to be the anterior edge of the ramus of mandible and the sternocleidomastoid muscle behind it; the lower edge of the zygomatic arch above it; the middle of the masseter muscle in front of it; and the body of the mandible in the area of its angle below it. The organ is typically divided into two parts: superficial and deep. The conventional line separating them is where the facial nerve passes through the parenchyma of the gland (Cilingiroglu Anli & Kazak, 2023; Ray & Soriano, 2023). The superficial lobe lies on top of the fibers of the masseter muscle in a thinner layer, while the deep lobe lies in the anterior part of the parapharyngeal space. It is surrounded by the posterior edges of the masseter and medial pterygoid muscles in front; the stylohyoid, styloglossus, and stylopharyngeus muscles on the side; and the fibers of the sternocleidomastoid muscle behind. The parotid salivary gland is surrounded by the parotid fascia, which forms a capsule around the gland (Hînganu *et al*., 2017; de Mello Gomes *et al*., 2019).

The boundaries of the fascia are noted as the mastoid process of the temporal bone from behind, the cartilaginous part of the external auditory canal and the zygomatic arch from above, the ramus of mandible from the front, and the line between the tip of the mastoid process and the angle of the mandible from below, and the superficial and deep leaves are distinguished within it (Andrew & Ewald, 2010; Sequeira *et al.*, 2010; Tsai *et al*., 2019). The posterior part of the fascia is closely adjacent to the main trunk of the facial nerve. This is significant because such a landmark facilitates locating important nerve structures during radical parotid gland operations (Varner & Nelson, 2014).

The superficial layer covers these structures from the outside. It is fixed to the lower edge and inner surface of the zygomatic arch. It continues into the deep temporal fascia. The deep layer lies in the innermost layers. It ends in the region of the stylomandibular ligament. This ligament is part of the ligamentous apparatus of the temporomandibular joint (Ochoa-Espinosa & Affolter, 2012; de Mello Gomes *et al*., 2019). Connective tissue partitions from both layers are woven into the gland's structures and are freely located among its parenchyma (Monkhouse, 1990; Sufianov *et al*., 2021). In addition to its two main parts, the parotid salivary gland often has processes. The superficial part has an upper (temporal) and an anterior (facial) process, while the deep part has a lower process and a pharyngeal process (Molinari *et al*., 2024). Due to the presence or absence of these processes, various configurations of the parotid gland are distinguished. This information is used in radiation diagnoses of parotid gland diseases and for correct orientation during surgical interventions. The temporal process is most often located in front of the cartilaginous part of the external auditory canal and extends slightly above it. The anterior process occurs on top of the bundles of the masseter muscle in 35-40 % of cases. The facial process is the most pronounced and widespread. It affects the contour of the salivary gland and is essential for the success of interventions (Jinnin *et al*., 2024).

Cases involving the facial process in salivary gland pathology are also often noted. Research by Ahn *et al*. (2017) shows that in 89.6 % of cases, the process is located between the anterior edge of the ramus of mandible and the masseter muscle. In the remaining cases, localization was observed outward from the masseter muscle (10.4 %). Additionally, there are cases of the anterior process being involved in the general pathology of the parotid salivary glands in 31.4 % of men and 25.1 % of women (McElwee *et al*., 2021; Jinnin *et al*., 2024). Thus, the importance of this formation in the gland's structure is evident. During surgical interventions in this area, care should be taken to monitor the presence of the thin branches of the zygomatic and temporal branches of the facial nerve. Damage to these branches can lead to impaired sensation in the corresponding areas (Turhal *et al*., 2023).

The ductal system of the parotid salivary gland plays a unique role in its morphology. It is generally assumed that the ducts comprise 5-7 % of the gland's total volume and are represented by two main types: striated and inset. The striated ducts have a wider lumen and large cells containing a large number of mitochondria. Inset cells have a smaller lumen diameter and smaller cell sizes. They are often covered with a layer of myoepithelial cells on the basal surface, which increases secretory activity in the presence of appropriate stimuli (Ahn *et al*., 2017; Reimnazarova *et al*., 2021; Kim *et al*., 2023).

The parotid salivary gland has a lobular structure. Many striated and intercalated ducts first assemble into intracellular ducts, which then assemble into intercellular ducts. The main duct of the parotid salivary gland, Stensen's duct, forms from these intercellular ducts. Some sources refer to it as the Stensen's duct (Davies *et al*., 2013). In their study, Richards *et al*. (2004) cite data indicating that the duct can also form from two or three main interlobular ducts that merge at the gland's outlet. In adults, this duct's length varies from 6.5 to 12 cm depending on skull type (brachycephalic or dolichocephalic) (Dumitru *et al*., 2024). The duct originates in the anteroposterior part of the gland and passes laterally in front of the muscular bundles of the masseter muscles. Then, it turns inward and passes through the fatty tissue of the cheek (Bichat's pouch) and the buccinator muscle. It opens on the mucous membrane of the oral vestibule at the level of the maxilla's second molars, forming a characteristic papilla. Evidence suggests that a number of buccinator muscle bundles are connected to the walls of Stensen's duct, which stimulates salivation during chewing (Hwang *et al*., 2005).

A conventional line on the skin is often used to visualize the structure and demonstrate the projection of the duct in the soft tissue of the parotideomasseteric region. There are three passage options: from the notch between the tragus and the antitragus to the nasolabial sulcus; from the notch to the lower edge of the ala of nose; and from the notch to the lateral commissure of the eyelid. Uzmansel *et al*. (2022) note that the first variant is predominant, with the proximal and distal points slightly higher than stated in 71.7 % of cases (Kochhar *et al*., 2016). However, some researchers claim that the duct is S-shaped, making it impossible to visualize as a straight line on the skin (Stram, 1972; Kainuma *et al*., 2010). This configuration significantly complicates endoscopic examination and

treatment, the preferred option for strictures and sialolithiasis (Reed *et al*., 2021). In the case of a tumor lesion of the duct, open access may be preferred. The duct's diameter in its proximal sections varies from 1.2 to 1.4 mm, with a narrowing of up to 0.5 mm observed in the mouth area (Kainuma *et al*., 2010). Often, an accumulation of parenchyma from the parotid gland is present in the upper part of the duct and is separated from its main mass. This accumulation constitutes an additional salivary gland, which occurs in 32-36 % of cases (Saint, 1951; Jinnin *et al*., 2024). Often, the tissue of the accessory salivary gland becomes a focus of various types of neoplasia (Ranly, 1998).

Topographic and anatomical relationships with vascular and nervous structures of the face

The facial nerve is one of the most closely related nervous structures to the parotid salivary gland, and its structure can vary significantly within the parotideomasseteric region. After exiting the stylomastoid foramen in the outer base of the skull, the nerve descends slightly. It is located medially from the inner part of the mastoid process. Then, it rises sharply. At the level of the lower edge of the earlobe, it weaves into the parotid salivary gland in an anterolateral direction. There, it divides into the temporofacial and cervicalfacial groups of branches. These branches form the parotid plexus, also known as the "pes anserinus major" (Witter *et al*., 2005). The temporofacial part then divides into two terminal branches: temporal and zygomatic branches. The cervical-facial part divides into three terminal branches: the buccal branch,the marginal mandibular branch, and the cervical branch, which are not part of the gland (Kim *et al*., 2023). The temporal branch passes through the parotid gland along the Pitanga line, exiting near the lower edge of the zygomatic arch (Ghassemi *et al*., 2003; Khan & Bagheri, 2014). The zygomatic branch runs along the line connecting the upper part of the nasal wing and the tragus from beginning to end. This line runs parallel to the zygomatic arch, sitting 1 cm below it (Khan & Bagheri, 2014).

The anatomy of the buccal branch, which contains three to four strong nerve bundles inside the gland, is closely related to the anatomy of its main duct, Stensen's duct (Rameh *et al*., 2008). Thus, in various anatomical cases, the buccal branch can exit the parotid salivary gland with the Stensen's duct, which is rare, or below it. In the latter case, it does not exceed a distance of 1-1.5 cm down from the zygomatic arch (Richards *et al*., 2004; Robardey *et al*., 2019). The buccal branch emerges from the anterior edge of the gland (Uzmansel *et al*., 2022). The marginal mandibular branch follows the lower edge of the mandible within the thickness of the parotid salivary gland. Surgical interventions on the parotid salivary gland are among the most challenging procedures in the head and neck region because damage to the facial nerve can seriously impair the patient's facial function. Due to the nerve's complex anatomy, surgeons must have a thorough understanding of its location and function to minimize injury risk. To prevent these potential complications, some researchers and practitioners recommend a more careful and precise approach to surgical planning, as well as the use of advanced imaging techniques and intraoperative monitoring. These measures can help ensure that the facial nerve is not damaged during the procedure and reduce the risk of long-term side effects (Arlt *et al*., 2022).

Anatomy of the external carotid artery and its branches

The external carotid arteries form as a result of the common carotid arteries bifurcating at the level of the upper edge of the thyroid cartilage or the body of the third cervical vertebra. The external carotid artery is initially located medially, on the outside of the sternocleidomastoid muscle, in relation to the internal carotid artery (Witter *et al*., 2005). After passing through the carotid triangle, the artery enters the inner surface of the stylohyoid muscle and the posterior belly of the digastric muscle, piercing the parotid salivary gland (Hwang *et al*., 2005; Hwang, 2014).

Upon reaching the level of the neck of the mandible, the external carotid artery divides into its terminal branches: the superficial temporal artery and the maxillary artery. Before dividing into these terminal branches, the external carotid artery gives off branches that combine into posterior, anterior, and medial groups (Rosa *et al*., 2020; Nikolenko *et al*., 2025). According to many sources, the parotid salivary gland is directly connected to the superficial temporal artery, the maxillary artery, the posterior auricular artery, the transverse artery of the face, and the retromandibular vein. The maxillary artery, one of the terminal branches of the external carotid artery, exits the parotid salivary gland through its medial part and splits into many branches in the pterygoid and infratemporal fossa (Pasick *et al*., 2020).

The superficial temporal artery originates among the parenchyma of the organ and gives off several parotid branches. It then exits the upper part of the organ and branches out in the temporal region. The transverse artery of the face branches off from the superficial temporal artery at the level of the temporofacial part of the main trunk of the facial nerve. It then continues as an upper and lower group of branches that extend from the parotid gland and

end in the area of the main duct. Sometimes, the transverse artery of the face does not give off large branches and ends within the gland. The posterior auricular artery sends a branch to the parotid salivary gland as well. The localization of the retromandibular vein is important in the anatomy of the parotideomasseteric region because it is a landmark for locating the main trunk of the facial nerve. The retromandibular vein, formed from the maxillary and superficial temporal veins, is a large vessel that passes through the posterior part of the parotid salivary gland, medial to the main trunk of the facial nerve. During operations in this area, defining the facial nerve becomes much easier after determining the location of the retromandibular vein (Hwang, 2014; Pasick *et al*., 2020; Rosa *et al*., 2020).

Clinical implications and applications

Thus, the embryonic development of the parotid salivary glands varies due to the numerous factors that regulate this process. Accordingly, the features of embryology give rise to different variants in the topographic and anatomical structure of the glands and the nearby structures of the parotideomasseteric region, as well as the elements of blood supply and innervation. Understanding all the nuances of these organs' development and structure provides opportunities for precise, high-tech manipulations in this region, which is considered one of the most complex anatomical areas.

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RESUMEN: La glándula salival parótida es una estructura crucial en la región maxilofacial que exhibe intrincadas relaciones anatómicas con elementos neurovasculares. Estas relaciones se ven influenciadas significativamente por el desarrollo embrionario. Este artículo resume el conocimiento actual sobre la embriogénesis, la organización anatómica y la relevancia clínica de la glándula parótida, haciendo hincapié en cómo los procesos de desarrollo determinan su morfología adulta. La glándula parótida se origina embriológicamente del epitelio oral ectodérmico entre las semanas 8 y 9 de gestación y experimenta una morfogénesis ramificada, regulada por factores de crecimiento (FGF, TGF y EGF), componentes de la matriz extracelular (colágeno III/IV y fibronectina) y mecanismos genéticos (p. ej., microARN-21). La formación del lumen impulsada por la apoptosis y la diferenciación de las células mioepiteliales refinan aún más la arquitectura ductal hacia la mitad de la gestación. Después del nacimiento, la hipoxia y las vías de señalización continúan influyendo en la maduración. Anatómicamente, la estructura lobulillar de la glándula está dividida en lóbulos superficiales y profundos por el nervio facial y exhibe variabilidad en los procesos (p. ej., temporal y facial) y en la anatomía ductal. La estrecha asociación de la glándula con el nervio facial, la arteria carótida externa y la fascia parotídea resalta la complejidad de la cirugía. La variabilidad topográfica, como la presencia de tejido glandular accesorio (prevalente en el 32 %-36 % de los casos) y los patrones de ramificación ductal, influyen en la precisión diagnóstica y terapéutica. Las correlaciones clínicas subrayan la importancia del conocimiento embriológico en el manejo de neoplasias, traumatismos y lesiones nerviosas iatrogénicas. Comprender los determinantes del desarrollo de la arquitectura glandular y las relaciones neurovasculares mejora la precisión de los procedimientos en cirugía maxilofacial y reduce la morbilidad. Esta revisión enfatiza la interdependencia de la embriología, la anatomía y la práctica clínica, abogando por un enfoque integrado para el manejo de la patología parotídea.

PALABRAS CLAVE: Glándulas salivales; Glándula salival parótida; Región parótido-maseterina; Desarrollo; Cirugía maxilofacial.

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