ULBS
Universitatea "Lucian Blaga" din Sibiu

Institute of Doctoral Studies

Doctoral School - Medicine

DOCTORAL THESIS

POSTOPERATIVE PARESIS OF FACIAL NERVE BRANCHES IN SALIVARY GLAND SURGERY (PAROTID GLAND, SUBMANDIBULAR GLAND)

SUMMARY

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Sibiu 2018

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The doctoral thesis includes a number of 258 pages, has an iconography consisting of 265 figures (photos and graphics) and 31 tables. The thesis is structured in three main parts: the general part, the special part and the bibliography. The bibliography contains 125 references from the literature. Key words: facial nerve, salivary glands, parotidectomy, postoperative paresis, House-Brackmann scale, medical treatment.

INTRODUCTION

One of the main problems of parotid and also submandibular salivary gland surgery is the discovery and isolation of facial nerve branches. Except in the case of malignant salivary gland tumors requiring the facial nerve sacrifice with tumor resection, special care should be taken for the intraoperative preservation of this nerve. However, usually after surgery on the large salivary glands in which the preservation of the facial nerve is intended, a postoperative degree of paresis of one or more variable length nerve branches is observed.

The research objectives are:

1). Determination of the incidence of facial nerve branches paralysis in salivary gland surgery according to pathology and type of surgery.

2). Evolution of the paresis in terms of pathology, type of surgery and adjuvant neurotropic treatment, drug (vitamin, NSAIDs, vasodilators) or physiotherapeutic. In addition, we aimed to make observations on the incidence of other nerve complications associated with parotid salivary gland surgery, Frey's syndrome and auricular lobe anesthesia following the segmentation of the large auricular nerve branches.

The final goal of the paper is to identify factors that can prevent nerve complications in salivary gland surgery and the optimal therapeutic attitude if they have occurred.

For my guidance over the years of study in project implementation, I express my thanks to my scientific coordinator Prof. univ. dr. Dan Sabau, Faculty of Medicine "V. Papilian "University," Lucian Blaga "University of Sibiu. I also wish to express my gratitude to Dr. Radu Ioan Neacsu, Oral Maxillofacial Surgery Department, the Emergency Military Hospital Sibiu, who helped me with my doctoral research.

CHAPTER I. Histological organization of the parotid gland, submandibular gland and peripheral nerves

Histological organization of the parotid gland and submandibular gland

The major salivary glands are the parotid gland, the submandibular (submaxillary) gland and the sublingual gland.(83)(17)(21) (46)

The small or minor salivary glands are spread in the oral mucosa. (83)

Supplemental glands of the digestive tract are the major salivary glands (parotid, submaxillary, sublingual), pancreas (exocrine and endocrine epithelial tissue) and liver (complex exocrine and internal secretory gland secreted by hepatocyte)(83)

Major salivary glands are delimited by a capsule and consist of secretory acins and a secretory duct system. (83)

The conjunctival capsule consists of collagen fibers, crosslinked fibers and adipose tissue. From the internal face of the capsule, trabecular or septal connective tracts that penetrate into the parenchyma and divide it into the lobes and lobules. In the capsule and in the intraparenchymatous septa, there are vessels and nerves. (83)

Histological organization of peripheral nerves

The peripheral (vegetative) nerves derive segmentally from the spinal cord via the union of the ventral and the dorsal roots. The ventral roots contain motor fibers originated in the motor neurons in the anterior horns, the dorsal conducting the spinning nerve fibers to the spinal cord. (25) The nerves are formed from nerve fibers disposed in parallel and longitudinal beams. (98) Nerve fibers are myelinic and amyelinic (rare). (98) (92)

M.O. on a cross-section, the nerve is wrapped and decomposed through connective tissue in a number of beads. (98) Nerve fibers in each beam are parallel and independent throughout the nerve, but they can pass from one beam to another. (98)

The connective tissue, which wears and divides the nerve fibers, is in relation to its disposition and its structure: the endonervus, perinervus and epinerv. (98)

CHAPTER II. Anatomy of the parotid gland, submandibular gland and facial nerve

Anatomy of the parotid gland

The parotid gland is symmetrical, bilaterally wearing the lateral and rear of the mandible, being located in the parotid region. (15) (23) The gland is divided into two parts by a fibrocellular plane through which the facial nerve passes and spreads:(103)

- The superficial side, lateral by the facial nerve, more voluminous.
- The deep part is deep.

Sometimes along the parotidian duct the presence of clusters of glandular parenchyma forming the accessory parotid gland (103) is found between the buccal branch and the zygomatic branch of the facial nerve. (61) The accessory parotid gland is localized previously by the main parotid gland between the zigomatic arch and the Stenon duct and is attached to the maseter muscle. (50)

Anatomy of the submandibular gland

The submandibular gland is inferior to the oral floor in the submandibular trough. It has a weight of 5-10g (103) (124), and a triangular prismatic shape, with rounded faces. Presents three faces and two extensions (103):

- The upper face is applied to the mandibular submandibular flap (103)
- The lower (external) face is covered by superficial neck structures (103)
- The medial face (internal) is applied to the suprahioid muscle (formed by milohioid muscles, hioglos, digastric, stiloglos and stilohioidian muscles) (103)
- The anterior extension starts from the medial face of the gland, accompanying the submandibular duct. If detached from the body of the gland, form the submandibular accessory gland. (103)
- The back extension is directed to the interglandular septum. (103)

The submandibular duct (Wharton's canal) is 5 cm long with a diameter of 2mm. (103)

The facial nerve (VII)

The facial nerve, the cranial nerve (encephalic) nerve, is intended for the innervation of the muscular skin of the face and throat. It is accompanied on the initial portion of its tract by the intermediate nerve. (103)

The apparent origin of the facial nerve is found on the anterior-lateral face of the cerebral trunk, at the level of bulbopontin, between the bulbous oval and inferior cerebellar peduncles, mediated by the apparent origin of the intermediate nerve and vestibulocohlear (VIII)(103)

Passage: the stilomastoid hole. (103) (30)

The tract of the facial nerve has three portions: an intracranial portion, an intrapathic portion, and an extrapolar portion. (103)

CHAPTER III. Physiology and pathophysiology of salivary secretion

Physiology of salivary secretion

Salivary secretion is produced by three pairs of salivary glands (parotids, submaxillaries and sublinguals) attached to the oral cavity, and to a lesser extent by small salivary glands in the oral mucosa. (40)

Chemical composition of saliva:

Saliva is an aqueous solution (98% water).

pH = 6-7 Organic and inorganic substances are dissolved in the saliva. (40) Inorganic substances are represented by various ions (K, Cl, HCO3, I, Na).

Organic substances are: (40)

- the mucus - provides adherence to the food particles and lubricates the food bowl, favoring swallowing.

-aglotinogens of the blood group AOB system are also present in saliva in 80% of the population.

- small amounts of substances that are eliminated by this route: urea, uric acid, lactic acid, creatinine.

- digestive enzymes: salivary amylase (phthylline)

Salivary amylase is secreted by the parotid glands (70%).

Mechanisms for the production of salivary secretion disorders

Salivary secretion has exclusive nerve adaptation mechanisms: the ascending paths of the impulses pass through the nerves: the tympanic, vague, glossopharyngeal, and the lingual and palatine branches of the trigeminal, the nerve centers have bulboprotubencial headquarters; the related pathways being parasympathetic and sympathetic(the main role in triggering and maintaining salivary secretion of the parasimpatic). (87) Salivary secretion may present quantitative or qualitative changes.

III.1. Immunological correlations

Parotid superficial nodes are located between the fascia and the gland; continues along superficial time vessels. The lymphatic vessels drain into the deep, intraparenchymatous parotid nodes in superficial and pre-uterine cervical lymph nodes, the vessels of the latter in the jugular lymph nodes (75). Within the gland, along the outer carotid and retromandibular vessels, there are 1-2 lymph nodes. Oral fluids are rich in immunoglobulins belonging to IgA and IgG isotypes. In serum, IgG antibodies are found to be at higher IgA concentrations. In parotide secretions, the IgA molecule concentration is nearly 500 times greater than that of IgG molecules. Approx. 95% of the saliva IgA molecules are produced locally by plasma from the salivary glands and not by those present in other secondary lymphoid organs (75). The submandibular nodes (5-12) are located within the submandibular trough, some in depth others above the gland. I get affections from: face, lips, nose, tongue and teeth. I send eferent vessels to the jugular chain (Bucur, 2003)

CHAPTER IV. Degeneration and regeneration of nerve fibers

Segmentation of a neural extension leads to the degeneration of the distal fiber and sometimes to the degeneration of the neural body - the Wallerian degeneration. (40)
This phenomenon was described from 1850-1852 by Augustus Volney Waller (1816-1870). (59) Regeneration - the proximal segment of the cut fiber begins to grow. The axon begins to sprout and gives rise to ~ 50 branches, one of which manages to penetrate into the tube formed by the cleared myelin sheath of the distal segment. Axoplasma grows slowly and if the distance between the severed ends is greater than 3 mm, it fails to penetrate into the distal myelin sheath, instead collapses and forms a small tumor called the neurom. (40)

Mechanisms of nerve regeneration. Factors that influence it

Regeneration of the peripheral nerves
Changes occurring after the breakdown of the axon continuity are:
- retraction of the proximal and distal ends
- accumulation of intraaxial organs by both parts of the section.
Factors influencing regeneration:
a). Intrinsec factors. The regenerative power decreases progressively with age. The rate of axonal regeneration may be influenced by a previous axonal lesion. (59)
b). Extrinsec factors. The quality and amount of regeneration is determined by:

- the composition of the regeneration environment,
- the restoration of contacts between the axonal buds and viable Bungner bands (59)

CHAPTER V. Systemic parotidomegaly

Sialadenosis (sialosis) is a noninflammatory disease, it can affect all salivary glands (occurs more often in the parotid level). Seizures and humoral transfer disorders occur in the glandular parenchyma, repeated swelling, variable in size but painless especially in the parotid gland. (49) Sarcoidosis is a systemic disease of unknown etiology. It is characterized by diffuse granulomatous infiltration of affected organs. (15)

Sjogren's syndrome is an autoimmune disease and affects women in decades 5-7 and appears to be a parotid level. Benign lymphoepithelial lesion. Most benign lymphoepithelial lesions appear as a component of Sjogren's syndrome, the clinical picture being specific to this syndrome. (15)

Benign lymphoepithelial cyst in HIV + patients. Approximately 3% of HIV-positive patients develop multiple intra-parathymic lymphoepithelial cysts.

CHAPTER VI. Tumor pathology of the parotid gland and submandibular gland

Benign tumors

Pleomorphic adenoma represents 45-74% of salivary gland tumors. (51) Pleomorphic adenoma is a mixed tumor due to the presence of epithelial and mesenchymal tissue. These tumors occur more frequently in the parotid gland.

The papillary chisthenolimphoma (Warthin tumor). Tumora Warthin was first described by Hildebrand in 1895. In 1910, Albrecht and Artz reported two tumors of the superior portion of the neck region they called papillary chisthenicum located in the lymph nodes.(81)

Basal cell adenoma is a rare benign tumor of the salivary glands, which can affect both the parotid and the small salivary glands (predominantly from the upper lip and less rarely from palatine fibroma)(15)

Oncocytoma is a rare benign tumor of the salivary glands resulting from the reactive proliferation of the oncocite. It occurs especially after the age of 50, being considered a hamartom developed against the backdrop of age-related canalic changes. (15)

Malignant tumors

Mucoepidermoid carcinoma is reported to be the most common. The salivary gland duct, consisting of several cell types, represents the histogenetic origin of mucoepidermoid

carcinoma. (91)

Acne cell carcinoma accounts for 1-3% of all salivary gland tumors. (6) Most cases are localized in the parotid gland (84%). The macroscopic aspect is variable on a case-by-case basis, the tumor can form a solid, microchicle, papillary-cystic or follicular mass. (6)

Cystic adenoid carcinoma was first described by Billroth in 1859 as the cilindrome. The term "cystic adenoid carcinoma" was introduced by Ewing (Foot and Frazell) in 1954. (107)

Mixed malignant tumor accounts for 3-12% of all salivary gland cancers. Most commonly occurs in the large salivary glands, and the malignant transformation of the mixed tumor occurs in 3-4% of cases (Bucur, 2003)

Well-differentiated polymorphic adenocarcinoma Cases with large salivary gland localization are sometimes the manifestation of pleomorphic exadenoma carcinoma. It occurs at the third age, somewhat more frequently in female sex. Clinically, a painless, slow-growing deformity occurs. In evolution, the lining of the lining is ulcerating, the tumor being over-infected. (15)

Secondary or metastatic malignant tumors in the salivary glands. Secondary forms most often affect the parotid gland. The primary tumor (spinocellular carcinoma, basal cell carcinoma, melanoma) is localized in the parotide-mazeterine region, the invasion of the gland being carried out directly by tumor infiltration.(15)

Criteria for the sacrifice of the facial:

The relative criteria for facial nodal sacrifice in parotidectomies for malignant tumors are (15):

• tumors with high malignancy;

• large malignant tumors (T3, T4);

• malignant tumors of the deep or extensive lobe in the deep lobe;

• recurrence of parotid malignant tumors (15).

The absolute criteria for the sacrifice of the facial nerve are: (15)

• Preoperative paresis in facial nerve area (one or more branches) - involves the sacrifice of the respective branches, or, as the case may be, of the n.

• one or more of the facial nerve branches pass through the malignant tumor mass (even if the patient does not have preoperative facial paresis);

• direct infiltration of one or more branches of the facial nerve, macroscopically visible intraoperatively;

• one or more of the facial n. branches pass at a small distance from the malignant tumor (macroscopically appreciable at about 2-3mm), which does not allow the free edges to be secured;(15)

CHAPTER VII. Surgical treatment of parotid gland tumors and submandibular gland

Surgery in total parotidectomy with facial nerve preservation: (89)

a). Total facial nerve conservation parotidectomy for benign or malignant tumors;
b). Total parotidectomy with facial nerve preservation for malignant tumors;
c). Total parotidectomy widened with facial nerve sacrifice for evolved malignant tumors associated with Neck-Disection widened loco-regional lymphadenectomy.
d). Total wound parotidectomy widened with facial nerve sacrifice, associated with extensive widening of the skin or other nearby anatomical formations (adherent tumors or skin ulcerations or invasions of neighborhood) and loco-regional lymphadenectomy of the Neck-Dissection type.
e). Treatment of recurrent parotid tumors (89)

CHAPTER VIII. Postoperative paralysis and facial nerve palsy

Facial area paresis occurs in the first 24 hours in cases where the dissection was laborious, bulky tumors, a parotid inflammatory history, reinterventions in which the trunk and the nerve branches could not be adequately treated. (89)
Systematisation of postoperative facial suffering by 3 degrees:
- grade III - complete paralysis
-grade II - facial motility present but significantly diminished
- grade I - does not involve the paresis but only the fall of the labial commission. (89)

VIII.1. The House-Brackmann classification and its modification for each ram of the facial nerve

The need to determine the prognosis of facial paresis and the treatment plan has led to the development of methods of quantification of this clinical condition.(34)
The main measure to classify the peripheral facial nerve paresis caused by a lesion in the trunk of the facial nerve is the House-Brackmann classification. This scale defines the normal function of the facial nerve with degree I to grade VI - almost no movement of the intact muscles. (101)
For the clinical evaluation, patients should: lift their eyebrows (the temporal branch), close their eyes (the zygomatic branch), wrinkle the nose, lips (the oral branch), open their mouth and show their teeth (the marginal branch of the mandible, the cervical branch).(101)

Because a single branch of the facial nerve is more frequently affected during an operation in the parotid / submandibular gland, and not all of them I have adapted this scale to track the evolution of the main branches.(71)

VIII.2. Drug treatment in facial nerve paresis

Taking into account the promising clinical results of the use of nimodipine in the treatment of peripheral paralysis of the facial nerve after a surgical approach; nimodipine may be recommended when the nerve is anatomically preserved. Its mechanism of action protects neurons and smooth muscle fibers from calcium overload and the following: swelling of the axons. (101)

Vitamin B6 (pyridoxine hydrochloride) in phosphorylated form is a cofactor for many enzymes involved in the metabolism of aminoacids.

Vitamin B12 (cyanocobalamin) participates in biochemical reactions: transport of methyl groups, synthesis of nucleic acids, proteins, metabolism of amino acids, carbohydrates, lipids.(80)

Benfotiamine as a liposoluble derivative of vitamin B1 (thiamine) is phosphorylated in the body with the formation of biologically active thiaminopyruvate and thiaminotriphosphate. In the pentose phosphate cycle, tiaminopyruvate participates in the transfer of aldehyde groups. (80)

VIII.3. Physiotherapeutic treatment in facial nerve paresis

1). Electrostimulation of denatured muscles after electro-diagnosis (less commonly used, may induce hypertonia and hemispasm)

2). Trophic facial massage and stimulant intra and extraoral

3). Automassage: is performed by the patient and constitutes the basic element of functional recovery

4). Thermotherapy: heating the skin of the area affected by paresis is done before the other physiotherapy procedures

5). Physical therapy: Avoiding the activation of the muscles in the lower part of the face as long as the muscles in the upper half are activated; asymmetric exercises can also be performed initially by the healthy part, then exercises at the level of affected hemiface or symmetrical exercises; use of whistling, blowing, masticatory exercises (Catan, 2010)

THE SPECIAL PART

I. MOTIVATION FOR CHOOSING THE RESEARCH TOPIC

Loss of facial nerve function is associated with a negative impact on the quality of life of the patient. In addition to functional problems, facial asymmetry and face inexpression reduces the psychosocial quality of the patient's life, it is therefore very important to quickly recover the postoperative facial nerve.

During surgery, facial nerve damage can occur by: pressure, crushing, elongation, ramming, deprivation of perinervous vascular sources. Local postoperative inflammation may also affect the facial nerve. Therefore, it is important to evaluate the risks of surgical intervention in the parotideusubmandibular area and to identify the ways to prevent and treat complications.

Both the physician and the patient should be advised about the possibility of these complications and their prognosis.

Knowing the natural (no treatment) evolution of postoperative facial nerve paresis is also useful in assessing the necessity and effectiveness of neurotrophic medication.

II. MATERIAL AND METHOD

In this paper we examined 25 patients admitted and treated in the Oro-Maxillofacial Surgery Department of the Emergency Military Hospital Sibiu for various pathologies in the territory of parotid and submandibular salivary glands involving the facial nerve.

The evaluation of these patients included the following steps:

- anamnesis
- preoperative clinical and imaging examinations
- postoperative clinical, imaging and histopathological examinations
- pre- and postoperative photostatic exam

Patient observation sheets of these patients were also consulted for the collection of identification, contact details, and information on surgical treatment (from the operative protocol), adjuvant drug treatment, and immediate postoperative progression.

CLINICAL STUDY:

The clinical study consisted in the evaluation and monitoring of facial nerve paresis patients admitted to the Oro-Maxillofacial Surgery Department of the Emergency Military Hospital in Sibiu between May 2012 and February 2018. The clinical study was conducted by prospective

examination of a 25- of patients who were called for control for functional reassessment of the facial nerve at 1 month, 6 months, 1 year, occasionally with observations on other possible postoperative nerve complications (affection of the large auricular nerve, Frey's syndrome) . Patients who did not show up under appointment were contacted by phone. Of the 25 patients, 2 of them were excluded from the full study (which would have assumed postoperative follow-up) because they did not show up until the first month and could not be contacted. Two other patients died in the postoperative clinical observation period of one year (one died at 5 months postoperatively, 2nd at 1 year postoperatively) due to neoplastic disease. However, these two patients remained in the study because it was considered in the case of the deceased patient at 5 months that the facial paresis was definitive as a result of a radical intervention of tumor resection in the parotid gland.

From the point of view of postoperative neurotropic adjuvant treatment, patients were divided into three categories:

I. Patients with irreversible facial paralysis / paralysis (after extensive tumor resections) (5 patients)

II. Patients without postoperative facial paresis (4 patients)

III. Patients with potentially reversible postoperative facial paresis (16 patients)

For patients in the first two categories, no adjuvant drug treatment was indicated (I category would have been obviously useless, in the second category unnecessary). For the patients of the third category, different treatments known as nerve regeneration aids (complex B vitamin therapy, Nimodipine vasodilator, Milgamma + Nimodipine, Milgamma + acupuncture, Alanerv + Neuroptimaizer) were applied randomly or no treatment.

For each case, a clinical study file was compiled summarizing all data from medical records (observation sheets, imaging examinations, laboratory), and clinical observations from postoperative controls. The data were then synthesized in a table and processed statistically.

III. PRESENTATION OF A CLINICAL CASE

The male patient B.V. aged 51 years living the Sibiu County, was admitted in the Department of Surgery of the Emergency Military Hospital Sibiu, in 2010 for multiple, subcutaneous tumour masses with lipomatous feature in the cervical and facial areas, and was clinically diagnosed with Madelung disease. In that clinical stage, the maximum size of the tumors was encountered in the anterior cervical area. For this reason, the first surgical approach, performed under general anesthesia, consisted in the excision of the anterior cervical lipomatous masses, which presented bilateral cervical extensions.(73)

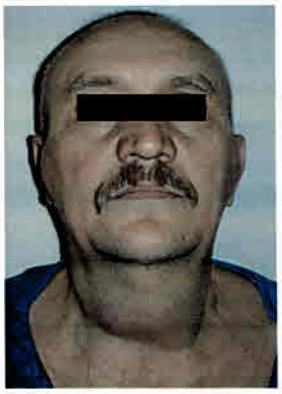


Fig. 1 *(casuistry Dr. Radu Ioan Neacșu, Dr. Adrian Popențiu) Pre-operative aspect (July 2010), frontal view: the maximum extension of the lipomatous tumours is in the anterior cervical area, but they are also extended bilaterally on both sides of the neck, in front of the sternocleidomastoid muscles.(73)

The immediate post-operative evolution was favourable, but the disease evolved progressively in the following 2 years and the tumour masses located in the submandibular areas became prominent and unaesthetic. The pacient was reoperated under general anaesthesia by a multidisciplinary team (General Surgery, Oral and Maxillofacial Surgery) and the operation consisted this time in the excision of the bilateral submento-submandibular lipomatous tumours. The patient presented transitory paresis of the marginal mandibular branches of the facial nerve which remitted after approximative 6 months without any medical treatment or physiotherapy.(73)

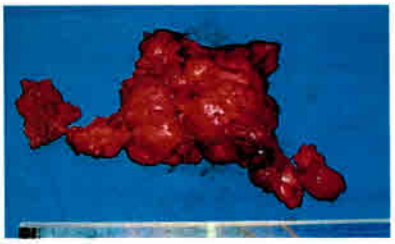


Fig. 2 * Excised lipomatous mass from submandibular region, histological founding lateral-cervical fibrolipomatosis (2012)(73)

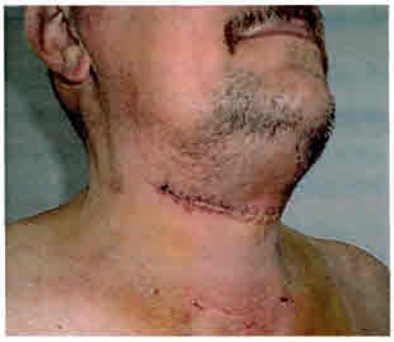


Fig. 3* The aspect of the post-operative wound after 1week, right half-view(73)

In 2012, in the Department of Oral and Maxillofacial Surgery the study of the post-surgical paresis of the facial nerve began, and the pacient was included in the database due to further progression of the disease. After the second intervention the lipomatosis continued its evolution and affected this time the parotid, occipital and bilateral posterior cervical areas causing difficulty in the head movement and aesthetic problems.(73)

Another surgical intervention was performed under general anaesthesia by the same multidisciplinary team (General surgery, Oral and Maxillofacial Surgery) and the excision of the parotid, occipital and posterior cervical lipomas was performed. The intervention was particularly difficult in the parotid regions where the identification of the facial nerve branches was necessary, which passed through the lipomatous masses at their exit from the parotid gland. On the left side, for security reasons the trunk of the facial nerve was exposed and after that the temporal - zygomatic ramifications. On the right side the identification of these branches was possible without exposing the nerv main trunk.(73)

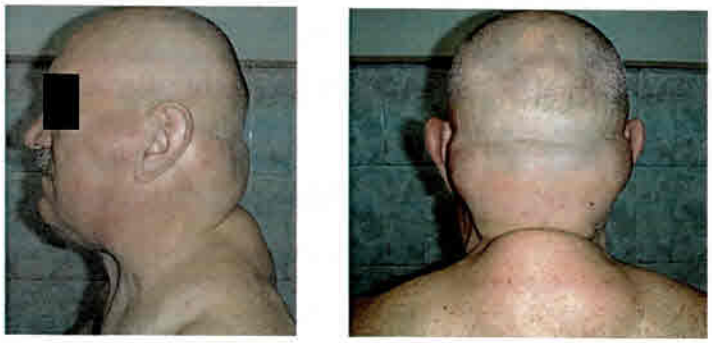
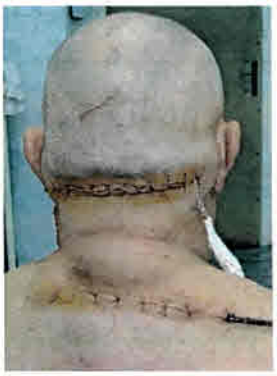


Fig. 4* Pre-operative aspect, left side (March 2014)(73)

Cervical-facial lipomatosis with progressive evolution after 2 years in the posterior cervical, occipital and bilateral parotid areas.(73)

Fig. 5* Pre-surgical aspect of the back (March 2014)(73)

The immediate post-operative evolution was favourable excepting a hematoma developed beside the left mandibular angle which asked for maintaining the drain tube 1 week for resolution. We also noticed the paresis of the temporal zygomatic branch of the facial nerve markedly on the right side Vth degree compared with IInd degree in the left side, according to the adapted House-Brackmann scale, probably due to the elongation of the nervous fibres during the dissection.(73)



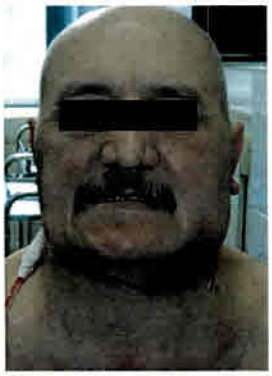


Fig. 6* (March 2014) posterior view. Aspect of the posterior cervical wounds 1 week after surgery(73)

Fig. 7* (March 2014) front view; 1 week after surgery: the cervical and the marginal mandibular branches of the facial nerve are bilaterally functional(73)

Fig. 8, 9* (March 2014) Post-operative aspect after 1 week, frontal view: Vth degree paresis of the right temporal-zygomatic branches of the facial nerve(orbicular muscle of the eye) according to the adapted House-Brackmann scale. The two photos, which were taken at few seconds interval show slow closing of the upper right eyelid.(73)

The patient was dosed after the surgery nimodipin tablets 60mg x 6/day for 7 days, then the evolution of the facial nerve's paresis was observed according to the current protocol. One month after surgery no improvement of the paresis was noticed,which remained Vth degree for the right temporal-zygomatic branch and IInd degree for the same branch on the left side.(73)

At the 6 month re-evaluation we noticed the complete remission of the bilateral paresis (Ist degree, adapted House-Brackmann scale accordingly).The patient returned for control examination 1 year and 8 month after the last intervention, when we found the normal functioning of the facial nerve and no progression of the cervical-facial lipomatosis.(73)

*(casuistry Dr. Radu Ioan Neacșu, Dr. Adrian Popențiu - Emergency Military Hospital Sibiu)(73)

IV. RESULTS AND DISCUSSIONS

There has been an almost unanimous practice of intervening with various drug or physiotherapeutic treatments considered beneficial to nerve regeneration in the postoperative facial nerve paresis. These types of therapies have been borrowed from the medical arsenal of other nerve pathologies (eg. Nimodipine in cerebrovascular disorders, complex B vitamins and steroidal anti-inflammatory drugs in inflammatory peripheral nervous disorders, physiotherapy in neuro-muscular disorders).

If for other nerve pathologies the efficacy of these treatments was more or less clinically proven, it was not well documented in the postoperative facial nerve palsy.

Nimodipine is known as a vasodilator by the L-type calcium channel blocking action with selective action on cerebral vessels. Different studies (Scheller et al., 2012) highlighted the beneficial effect of administering this drug to lesions of the intracranial portion of the facial nerve. It was proposed by Scheller et al., 2012 to use nimodipine and to accelerate the recovery of the facial nerve function after its intraoperative injury. However, the study published by the anterior mentioned authors is based only on observations on a small group of patients (13 cases) with different degrees of facial postoperative paresis, all of whom were treated with nimodipine without the control group. Consequently, the findings on the acceleration of nerve function recovery under Nimodipine treatment can not be considered valid.

A 2008 study (Roh et al., 2008) conducted on two groups of patients with facial paroxysmal parotidectomy in which the first group of Prednisolone administered the second control was the ineffectiveness of corticosteroid treatment in the faster recovery of facial nerve function.

Most studies show that the functional period of the facial nerve regeneration after surgery is between 6 and 9 months (Jain et al., 2004) without any adjuvant treatment, which shows that there is a natural nervous repair potential whose mechanisms are to date incompletely known.

In view of these considerations we have chosen a maximum of 1 year dispensary period with immediate postoperative controls at 1 month - 12%, 6 months - 16%, 1 year - 72% (Table 3, figure 235) . We also considered it strictly necessary for validation of the result and comparison with a non-treated control group.

Most patients (18 out of 25) could be followed throughout the dispensary period and were able to statistically process the data. However, some observations could also be made in patients who could not be followed at 1 month and 6 months. Most patients enrolled in the study were over 35 years of age, consistent with age of chronic and chronic inflammatory

pathology (Table 4, Figure 236). Of the 2 (8%) patients under the age of 35, one had a congenital odontogenesis disorder (complex odontom associated with secondary aneurysmal bone cyst lesions), and the second had a pseudo-chronic chronic sialadenitis.

The young age of the patient with the complex odontom associated with secondary lesions of aneurysmal bone cyst (13 years) was probably an important factor contributing to the rapid regeneration not only of the facial nerve but also of the lower alveolar nerve that required neuron after tumor resection.

We included not only partial or total parotidectomy for parotid tumors but also various pathological conditions that involved interventions in the peripheral branches of the facial nerve (fibrolipomatosis, submandibular gland inflammation, latero-cervical adenopathy, jaw bone pathology) (Table 5, Figure 237). This is reflected to a certain extent in the higher frequency of damage to the marginal ram of the mandible after surgical interventions.

It should be noted that fibrolipomatosis (12.5%), a benign condition and apparently easy to approach surgically when advanced stage diffuses infiltrates S.M.A.S. and parotidian fascia respectively to the glandular parenchyma, which makes it necessary to identify, isolate and dissect the facial nerve as in a parotidectomy intervention.

From the correlation of the obtained data correlated with the histopathological type with the sex of the patients in the study (table no.6, figure 238), we observe a predominance of female sex in the case of monomorphic and pleomorphic adenomas and salivary glandular cilia or male gender in parotid carcinomas and tumor Warthin, fibrolipomatoidosis associated with chronic alcohol consumption and latero-cervical adenopathy (in the context of smoking and chronic alcohol consumption), which is consistent with the epidemiological data known from the literature (15)

Regarding the type of surgery (Table No. 7, figure 239), in most patients the side parotidectomy intervention was performed - 52% (the excision of the tumor along with the superficial lobe of the parotid gland) always with the intention of preserving the facial nerve. In the case of total parotidectomies - 12% these were used for malignant tumors (2 cases: 1 case with known histopathological diagnosis, the second with very suggestive clinical data for a malignant tumor) and a case of benign tumor with parapharyngeal extension. Partial facial nerve preservation was achieved in the second case of parotid malignant tumor and the quasi-complete preservation of the facial nerve in the case of the bulky tumor but where a neuroraphy was practiced for an accidentally sectional ram.

- Subtotal parotidectomas were considered - 8% always with the intention preservation of the facial nerve interventions in which a small part of the glandular acini was preserved (1 case of

recurrent tumor in the multinodular form and a case of deep lobe tumor) In case of cervical (1 case - 4%) and the excision of latero-cervical adenopathy blocks (2 cases - 8%), the marginal branch of the mandible was preserved only at radical cervical evidence. The decision to conserve this nerve is taken intraoperatively depending on the ratio of the nerve to the adenopathic block. For the excision of the latero-cervical lipomatous formations of Madelung disease, the isolation of the trunk and the intra-parotid branches of the facial nerve in one unilateral left case was chosen, in the remaining cases (the first contralateral right case, the second bilateral case), the dissection of the facial nerve threads at the exit from the parotid region, which increased the difficulty of the intervention, but the parotid gland. In one case (4%), submaxylectomy was performed for an apparent posterior posterior cystic form of the submaxillary gland in which the marginal branch of the mandible was preserved with / without the cervical-facial branch presenting a close relationship with the cystic formation. In one case (4%) (in a patient with odontogenic tumor of the mandibular angle) segmental resection of the angle and the mandibular body was performed by cervical approach with the preservation of the marginal branch of the mandible but with its intraoperative trauma by traction of the flap. In this case it was reintervented after 7 months for the ablation of the mandibular osteosynthesis material, but the dissection of the marginal branch of the mandible was this time made more difficult by the postoperative scar.

In general, surgical interventions were made with the intention of preserving the facial nerve (Table 8, figure 240) only in four cases one or more branches being deliberately sacrificed (a case of malignant tumor of the recurrent parotid region - all branches two cases of latero-cervical metastatic adenopathies are sacrificed - the marginal branches of the mandible and the cervico-facial branch, and a case of chronic parotiditis where the dissection was significantly impeded by the intraglandular inflammatory fibrous tissue that forced the marginal branch of the mandible to be sacrificed.

In interventions in which the preservation of the facial nerve was tempted, this was accomplished in most cases except:

- the case of a large parafaringian bulky tumor in which the marginal branch of the mandible that was repaired after the excision of the tumor by neuroraphy was accidentally cut,
- the case with the mandibular tumor, which was reintervented after 7 months when it was not possible to reveal in the scar tissue the marginal branch of the mandible
- the case of the parotid tumor biopsy extended in the carotid trine, when also during the surgical resection for the tumor excision it was difficult to highlight the marginal branch, accidentally dilated and repaired by neuroraphy

- the case with parotid tumor recurrent in the multinodular form in which surgical trauma during dissection through scar tissue (elongation, crushing) was more important.
Also extremely thin nerve threads with minimal intake to facial neuromotor function were often dilated during dissection, clinical consequences being insignificant.
We have made observations during the postoperative clinical follow-up period and in terms of restoring the sensitivity of the facial region and the auricular lobe depending on whether or not the two branches of the large auricular nerve are conserved, as well as the incidence of Frey's syndrome depending on whether or not the fascia is preserved superficial parotid (SMAS).
Thus we noticed the early restoration of the skin sensitivity of the parotideomaseter region even though the anterior ankle of the large auricular nerve was sacrificed in all cases and the persistence even after one year of a degree of hypoaesthesia of the auricular lobe in the cases where the posterior ram was sacrificed of this nerve.
We recorded three cases with Frey's syndrome of 11 cases in which the external parotid strain was not preserved, of which 2 did not require therapy and the symptoms were tolerated by the patients, and in the other case, local treatment with scopolamine ointment was not prescribed to control).
Regarding the facial nerve paresis associated with preexisting or postoperative affection (Table 9, figure 241), we found that in all 3 cases - 12% with the existing preoperative paresis, it was maintained postoperatively during the dispensary period (2 cases of malignant tumor followed one year, respectively 6 months and 1 case of parotid cyst in an elderly patient followed one month). Of the other cases, the majority (18 - 81.81% out of 22) experienced a degree of paresis of one or more nerve branches that were followed over a period of one month to one year, the majority (14 cases) for one year . Only these 14 cases were considered for the statistical calculation of adjuvant neurotropic efficacy.
Favorable progression with / without treatment of complete remission of paresis (Table 10, Figure 242) was considered. An improvement in the facial nerve function up to the second degree was considered a partially favorable progression and those without any improvement or only a slight improvement in unfavorable progression. Overall, we observed a favorable trend in most patients (9 - 64.28% and 3 - 21.42% of 14 dispensaries for one year). The two unfavorable evolutions (14.28%) were represented by a deliberate sacrifice of the marginal branch of the mandible for chronic parotid inflammation with abundant fibrous tissue and a case of reintervention in the marginal branch of the mandible. This shows that the evolution of the paresis is generally good if the facial threads are only elongated or crushed

intraoperatively without being fully dilated and if they were cut and could be used immediately the neurorafia evolution was also good (1 case favorable evolution, 1 case partially favorable evolution to this last situation). Out of the 25 patients enrolled in the study, 10 adjuvant neurotropic treatment was administered to 10 cases with different postoperative facial nerve palsy (Table 11, figure 243). Of these 10 cases, 3 cases were eliminated for the final statistical calculation due to the insufficient follow-up period.

In the remaining 15 patients (60%) with or without paresis, no treatment was given, 3 of which had cancers for which the surgery involved facial nerve sacrifice, 4 cases without paresis which obviously did not require adjuvant treatment and 8 cases with paresis which were considered for the comparative statistical study. Of these last 8 cases, 1 was removed due to insufficient tracking time.

This resulted in 2 groups of patients with 7 cases with postoperative facial nerve paresis followed for one year: 1 lot receiving a specific adjuvant neurotropic treatment and 1 control group without any treatment. Adult neurotropic treatment: Milgamma- 1 case (4%), Milgamma + Nimodipine- 3 cases (12%), Milgamma + acupuncture- 1 case (4%), Nimodipine- 3 cases (12%), Alanerv + 2 cases (8%). For Nimodipine, it was administered at a dose of 6 x 60 mg 7 days versus 10-14 days as was the duration of administration in the study published by Scheller et al., 2012, from caution to avoid a potential hypotensive effect. These drugs were administered in a randomized manner, with only one patient opting for acupuncture. However, there has been a tendency to prescribe such treatment in patients with a higher degree of paresis.

In order to find out the frequency of damage to each facial nerve ram (Table 12, figure 244) versus the total number of cases that showed a certain degree of postoperative paresis we eliminated the 4 cases that did not show any paresis and 2 more already had preoperative paresis due to malignant tumor progression or previous surgery. Thus, we identified 19 patients who have been seen for control at least one month, to which we noticed that the most affected ram was the marginal branch of the mandible. The cervical-facial branch was considered together with the marginal branch of the mandible in a functional motor unit because the platisma (inervated by the cervical-facial branch) contributes equally to the depressive muscles of the lip and the mouth of the mouth at the lowering of the angle of the mouth, a distinction can be made between affecting one or the other.

But in 19 patients with postoperative paresis, interventions other than parotidectomies (14 parotidectomies, 2 adenopathic block excision, 1 fibrolipomatosis excision, 1 submaxylectomy, 1 mandibular segmental resection) were performed.

Only the cases in which the parotidectomy was performed (18 patients)(Table No. 13 ,Figure 245) we observed that the entire marginal branch of the mandible with / without the cervical branch was the most affected (84.21%), followed by the oral branch (44.2%), the temporal branch (36.84%) and the zygomatic branches (21.05%), which in the case of the marginal branch of the mandible corresponds to the known statistical data (113).

An explanation for the fact that this ram is most effective is the location of the tumor in the thickness of the parotid gland that most commonly occupies the lower pole of the gland, and there is an anatomical space whose walls with fewer muscular or osteotoninous elements allow tumor growth through tissue distention.

Another explanation for the more frequent observation of the lowering of the angle of the mouth can be the cutting of the posterior moss fibers during dissection, even without the intraoperative damage of a nervous ram.

We analyzed the evolution of the paresis for each ram (marginal margin of the mandible, Table 14, Figure 247, Table No. 15 Figure 247, Table No. 16 Figure 248, Table No. 17 Figure 249, Table 20, figure 25, group 20), grouping the patients initially into paired groups according to the adjusted House-Brackmann scale, and noting how the composition of each group changed over time. Although the total number of cases observed decreased for 6 months and one postoperative year for different reasons (death, default) we took into account the proportion of different paresis groups.

I have generally noticed that the functional improvement of all nerve branches, regardless of the initial degree of the paresis.

Because of the small number of cases, we did not take into consideration here the comparative study of patients who received adjuvant drug treatment against a untreated control group. For 3 of the 4 categories of branches (the marginal branch of the mandible - table no.21, fig.253, 254, the buccal branch - table no.22 fig.255, 256, zygomatic - table no.23 fig.257, 258) because the temporal ram paresis was encountered in very few cases, we made a graph of the evolution of the average degree of paresis calculated for each moment of dispensarization (immediately postoperatively, 1 month, 6 months, 1 year).

All three graphs of the evolution of the paresis on branches have a similar configuration. The first portion of the graph is downward (up to 1 month) then has a steep downward slope to 6 months after which the slope again becomes smooth until 1 year. This shows that morpho-functional recovery of the facial nerve after an operative trauma takes place for the most part in the period of 1 month to 6 months.

Of the 25 cases initially studied, we were able to keep 7 paresis patients who received a

specific treatment for the final analysis of the paresis evolution (Table 25, figure 261, 262) and 7 patients with paresis without any treatment (table 26, 263, 264). Although 3 of these cases could not be tracked for 6 months, one-year follow-up was extrapolated because at 6 months there was paresis of Grade I after the House-Brackmann scale (full recovery). For each of these two lots, we plotted the evolution of the average degree of paresis. These graphs show a similar configuration to the ones outlined above. Analyzing the average graphs for the two groups, we observe a better but statistically insignificant evolution in patients who received some adjuvant treatment (Table 27, figure 265). Consideration should be given to the interpretation of these evolution charts, the fact that in the control group there was a case in which a facial nerve ram had been intraoperatively cut and neurorafia (No. 1 in Table 26) could not be practiced. This single case whose prognosis was unfavorable with / without treatment altered the mean paresis score to 1 year for the control group. This situation has not been met in the treated group of patients. If we remove from each lot the extreme cases (with a high average of the paresis at 1 year) and no. crt. 2 of Table no. 25 and no. crt. 1 of table no. 26 we get an average of 1 year for the first batch of 1.08 compared with 1.17 for the control group, a statistically insignificant difference.

V. CONCLUSIONS

I. As regards the first objective of the study we could determine, on the group of 25 patients followed over a period of 5 years, the frequency of damage to each of the 4 major divisions of the facial nerve (marginal margin of mandible + cervical r, r , buccal, temporal, zygomatic) respectively:

1). Global regardless of pathology and type of marginal mandibular + cervical surgery (84.21%) was the most affected, followed by oral rat (44.2%), yr. zigomatic (36.84%) and temporal (21.05%).

2). The same order of frequency was also maintained for the strict pathology of the parotid salivary gland for which variants of parotidectomies were performed (marginal mandibular + cervical rhythm - 77.78%, oral - 55.56%, r. temporal - 44.44%, zigomate - 27.78%).

II. Regarding the second objective of the paper, the relatively small number of cases (due to their rarity) with different pathologies did not allow to find results with statistical significance. We could, however, make observations that we considered important for the clinical attitude towards the risks and evolution of postoperative facial nerve paresis as follows:

3). Functional recovery of the facial nerve takes place for the most part within one month - 6

months postoperatively regardless of whether the patient received adjuvant treatment or not.
4). Adjuvant neurotropic treatment (vitamin B complex, Nimodipine, physiotherapy) does not appear to have a beneficial effect on the development of the paresis. To validate this observation, the number of patients in each batch should be (treatment and control should be at least 21).
5). The most important factor influencing the degree and evolution of postoperative paresis is the magnitude of operator trauma on the facial nerve. A dilated or severed nervous ram for which neurorafia is not immediately practiced has a poor progression. Cases where neuroraphy has been practiced have been partially favorable. Elongation or deprivation of nutritional intake (skeletal nerve) affects the nerve to the smallest extent.
6). We noticed a worse evolution of the paresis in case of surgical reinterventions and if there is a facial nerve too much (malignant tumor, chronic inflammation).
7). We recorded 2 cases of Frey's syndrome in 14 patients who did not conserve S.M.A.S. and in the four patients in whom it was conserved, there was no case of Frey's syndrome. This shows the importance of preserving the external parotid fascia when possible.
8). Auricular lobe anesthesia was a rather common complication after parotidectomy, and recovery of sensitivity was slow and only partial during the 1-year follow-up period.
9). Age of patients may be a factor influencing nerve healing after surgery. We could not draw any conclusions because one young patient (13 years of age) was studied in this group of patients in whom a complex intervention was performed using the reconstruction of the mandibular body with the titanium reconstruction plate and the alveolar nerve neurora inferior, a spectacular bone regeneration along the periostal sleeve around the unformed mandibular canal was observed by keeping the lower alveolar nerve continuity as well as the quasi-complete recovery of sensitivity to the lips.
III. Regarding the way of working in this study we can make the following findings:
Positive aspects:
10). It was a prospective study with factsheets, organized with clear guidelines.
11). I modified the House-Brackmann scale by adapting it to each nervous ram in part to increase the fidelity of clinical records. However, we consider it inappropriate to note the degrees of paresis from I to VI in which degree I means lack of paresis = normal, more suggestive would be that the absence of the paresis is marked with grade 0 and the maximum degree is V.
12). We have applied a statistical study to two groups of patients in which a control group was essential to draw conclusions on the efficacy of adjuvant neurotropic treatment as opposed to

the study published by Scheller on the treatment of nimodipine for postoperative facial nerve paresis lacking control lot.

Negative issues:

13). The group of patients studied was insufficient as a number (due to their rarity) to draw statistically significant conclusions for each treatment. An alternative would be to prescribe one type of treatment (Nimodipine only, only vitamins or physiotherapy only)

14). A more frequent dispensing of cases including 2 and 4 months postoperatively would have provided more information on the evolution of the paresis.

15). Results with a higher degree of statistical significance we would have obtained in a multicentric study (all cases were admissions to the Oral Maxillofacial Surgery Department of the Emergency Military Hospital Sibiu).

Proposals for further research:

1). Extend the study to a larger number of patients (possibly multicenter) that separately targets different adjuvant drug therapies.

2). Correlation of clinical research with laboratory research to identify the biochemical mechanisms underlying nerve fiber regeneration that may have clinical use.

BIBLIOGRAFIE

1). Abrahams P.H., Hutchings R. T., Marks Jr.S.C. (1999) *"McMINN Atlas de anatomie a omului"* Ed. All Educational, Bucureşti.

2). Albu E., Mungiu O. (2007)*"Elemente de farmacologie clinică"*, Casa de Editură Venus, Iaşi, p.186, 189.

3). Al-Khtoum N., Qubilat A., Al-Zaidaneen S., Al- Sarhan M., Al-Qudah A. (2013) *"Clinical characteristics of pleomorphic adenoma of salivary glands among Jordanian patients"* Salvat in data de7.03.2014 de pe adresa http://www.jpma.org.pk/full_article_text.php?article_id=4062

4).Al-Noury K., Lotfy A. (2011) *"Normal and pathological findings for the facial nerve on magnetic resonance imaging"*, Clinical Radiology, Elsevier,66, p.701-707.

5). Anderson J.(2011) *"Celiac Disease and Sjongren Sindrome"* Salvat în data de 28.07.2012 de pe adresa http://celiacdisease.about.com/od/commoncomplicationsofcd/a/ Celiacdisease-Sjogren-Syndrom.htm.

6). Asaf S., Tuvia A. (2011) "*Patologia unor tumori selectate ale glandelor salivare.*" Medical Connections, nr. 3(23), p.97-98

7). Baciu I. (1977) "*Fiziologie*" Ed. Didactică şi Pedagogică, Bucureşti, p.46, 192, 145-147.

8). Bailey R. *"Salivary Glands and Saliva"* Salvat în data de 28.07.2012, de pe adresa: http://biology.com/od/humananatomybiology/ss/salivary-glands-and-saliva.htm.

9). Bakshi J., Budhiraja G., Gupta K., Patro S. K., Gupta N. (2012) *"Epithelial-Myoepithelial Carcinoma Of Parotid Gland – A Surprising Clinical Entity"*, Surgical Science, 3, 274-278.

10). Batori M., Mariotta G., Giovannone G., Casella G., Casella M.C., *"Warthin's tumor of parotid gland: treatment of a retroneural lesion by enucleation"*, European Review for Medical and Pharmacological Sciences 2002; 6: 105-111

11). Borundel C. (2007)*"Medicină internă pentru cadre medii"*, Ed. BIC ALL, Bucureşti, p. 559, 804.

12).Botezan A., Stanilă A., Mihu E. D. (2011) *"Managementul lagoftalmiei paralitice"* ACTA MEDICA TRANSILVANICA, Sibiu, 2(4)47-48.

13). Bucur A., Dincă O., Ionescu H.(2007) "*Adenom pleomorf parotidian gigant - prezentare de caz şi recenzia datelor din literatura de specialitate.*" Chirurgia,102(3):363-366

14). Bucur A. (coord.), Chirilă L., Ciocan L., Dincă O., Ghiţă V., Ionescu H., Niţa T., Pădurariu C., Popovici F., Totan C. (2007) *"Tratat de chirurgie Sub redacţia: Irinel Popescu Vol. III Chirurgie oro-maxilo-facială"* , Ed. Academiei Romane, Bucureşti, p. 353.

15). Bucur A., Vila N. C., Lowry J., Acero J. (2009) "*Compendiu de chirurgie oro-maxilo-facială"* vol. II. Ed. Q Med Publishing, Bucureşti, p. 716, 744-748, 758-795.

16). Burlibaşa C., Chirilă L., Ganută N., Gogalniceanu D., Herescu C., Lung T., Maftei I., Pricop M., Rotaru A., Supaţeanu M., Urtilă E., (2003) "*Chirugie orala şi maxilofacială"* Ediţia a II-a. Ed. Medicală, Bucureşti, p. 1148,1152.

17). Carlson J., Licitra L., Locati L., Raben D., Persson F., Stenman G.*"Salivary Gland Cancer: An Update on Present and Emerging Therapies"* Salvat in data de 4.03.2014 de pe adresa http://meetinglibrary.asco.org/content/275-132

18). Casanova Egon R. *"Parotid Gland Non-Hodgkin Lymphoma-Malt-Type. Clinical Case Molecular Analysis"*. Chile. Salvat în data de 30.07.2012 de pe adresa http://www.egoncasanova.cl/cmlpaper.html

19). Chedid H.M., Rapoport A., Aikawa K. F., Menezes A. S., Curioni O.A. (2011) *"Warthin's tumor of the parotid gland: study of 70 cases"*, Rev. Col. Bras. Cir. 38 (2): 90-94.

20). Cheung M., Franzmann E., Sola J., Pincus D., Koniars L. (2011) *"A Comprehensive Analysis of Parotid and Salivary Gland Cancer: Worse Outcomes for Male Gender"*, Journal of Surgical Research 171, p. 151-158.

21). Chi T.-H., Chen H.-S., Yuan C.-H., Tsao Y.-H. (2013) *"Deep Lobe Parotid Abcess with Facial Nerve Palsy: A Case Report"*, West Indian Med. J., 62 (9): 856.

22). Chirilă M., Mureşan M., Bolboaca S. (2014) *"Study of Preoperative Predictive Signs in Management of Facial Nerve in Parotid Tumors"*, MAEDICA – a Journal of Clinical Medicine, 9 (1): 39-43.

23). Chu A., Kirsch C., St. John M. (2011) *„Severe compression injury of the soft tissue of the parotid"*, International Journal of Pediatric Otorhinolaryngology Extra 6, p. 114-115

24). Chua D. Y. K., Goh C. H. K. (2014) *„Parotid Gland Surgery for Benign Tumors: Have we Come Full Circle?"*, Proceedings of Singapore Healthcare, vol. 23, nr.1.

25). Ciurea V. (coord.), Constantinovici A., Danăilă L., Brehar F., Ciubotaru V., Coman T., Davidescu H., Exergian F., Florian I., Gorgan R., Gramadă F., Iacob G., Ianovici N., Iencean Ş., Iliescu A., Ogrezean I., Perin R., Podea M., Poeată I., Popa C., Stan H., Stoica F., Szabo B., Szabo I., Taşcu A. (2007) *"Tratat de chirurgie Sub redacţia: Irinel Popescu Vol. II Neurochirurgie"* , Ed. Academiei Romane, Bucureşti, p. 385-392.

26). Cristofaro M. A., Allegra E., Giudice A., Colangeli W., Caruso D., Barca I., Giudice M. (2014) *"Pleomorphic Adenoma of the Parotid: Extracapsular Dissection Compared with Superficial Parotidectomy – A 10- Year Retrospective Cohort Study"*,Hindawi Publishing Corporation The Scientific World Journal

27). Cuparencu B., Szegedi L., Maghiar A. (1998) *"Farmacologie clinică pentru anestezişti"*, Ed. Librariile Crican, Oradea, p. 195.

28). Dmytriw A., Gullane P., Bartlett E., Perez-Ordonez B., Yu E. (2013) *"Parotid gland metastasis originating from malignant meningioma"*, Clinical Imaging, Elsevier, 37, p. 740-743.

29). Dumitrache M., Stanilă A.,Voinea L., Filip M., Nicula C., Potop V., Talu S., Balta F., Ciocalteu A. M., Dobre X., Tataru C. P. Anitescu M., Arsene C., Alexandrescu C., Mocanu B., Stanca H., Dascalu A. M., Burciu R., Cioboata M., Dima A. M. Filip A. Lascu R., Teodorescu L., Stefaniu G. I. (2012) *"Tratat de oftalmologie – Vol. I, II"*, Ed. Universitară "Carol Davila", Bucureşti, vol. I-p.352, vol.II-p.603.

30). Ellis H. (2012)*"Anatomy of the salivary glands"*, Basic Science, Surgery, Elsevier,30:11, p.569-572.

31). El Shahat H., Fahmy H., Goudar G. (2013) *"Diagnostic value of gadolinium-enhanced dynamic MR imaging for parotid gland tumors"*, The Egyptian Journal of Radiology and Nuclear Medicine 44, p. 203-207.

32). Fakhry N., Antonini F., Michel J., Penicaud M., Mancini J., Lagier A., Santini L., Turner F., Chrestian M. A., Zanaret M., Dessi P., Giovanni A. (2012) *"Fine-needle aspiration cytology in the management of parotid masses: Evaluation of 249 patients"* European Annals of Otorhinolaryngology, Head and Neck diseases 129, p. 131-135

33). Fareed M., Mowaphy K., Abdallah H., Mostafa M. (2014) *"Temporary facial nerve paralysis after parotidectomy: the mansoura experience, a prospective study"*, Egyptian J. Surgery 33:117-124.

34). Fonseca K. M. O., Mourao A. M., Motta A. R., Vicente L. C. C. (2015) *"Scales of degree of facial paralysis: analysis of agreement"*, Braz. J. Otorhinolaryngol., 81 (3): 288-293.

35). Fuchsmann C., Viremouneix L., Collardeau-Frachon S., Bouvier R., Guibaud L., Froehlich P. (2011) *"Management and treatment of a sialoblastoma of the submandibular gland in a neonate: Report of one case"*,

International Journal of Pediatric Otorhinolaryngology Extra 6, p. 168-171.

36). Gaje P., Raica M., Mederle O.(2010) *"Histologie orală Ce trebuie să ştie studentul de Anul I în Medicină Dentară"* Litografia UMF, Timişoara, p. 97, 104-105

37). Ganuţa N., Bucur Al., Vârlan C., Malita C., Ioniţă S., Petre A. (1999) *"Urgenţele în stomatologie şi chirurgie oro-maxilo-facială"* Ed. Naţional, Bucureşti.

38). Ganuţă N.,Bucur A. (2003) *"Chirurgie maxilo-facială"* Curs. Ed.Naţional , Bucureşti, p.298-300, 304, 306-308, 309, 311, 313-317.

39). Garcia-Purrinos F. J. (2011) *"Thirteen years` experience with superficial partial parotidectomy as treatment for benign parotid tumors"*, Acta Otorrinolaringol Esp.,Elsevier Doyma, 62 (1), p.10-13.

40). Grama M. (1994) *"Curs de fiziologie Vol. I"*, Ed. Hermann, Sibiu, p.81

41). Grama M., Grosu F. (2002) *"Fiziologie – Curs"*, Ed.Alma Mater, Sibiu, p.80, 81, 132-138.

42). Guggenheimer J., Close J., Eghtesad B. (2009) *"Sialadenosis in Patients with Advanced Liver Disease"*, Head Neck Pathol. 3(2), p.100-105.

43). Gupta S., Mends F., Hagiwara M., Fatterpekar G., Roehm P. C.(2013) *"Imaging the Facial Nerve: A Contemporary Review"*, Hindawi Publishing Corporation, Radiology Research and Practice.

44). Hajiioannou J., Floru V., Kousoulis P., Kretzas D., Moshovakis E. (2013) *"Reversible facial nerve palsy due to parotid abcess"*, International Journal of Surgery Case Reports 4, 1021-1024.

45). Hirokava N., Hareyama M., Akiba H., Satoh M., Oauchi A., Tamakawa M., Sakata K., Nagakura H., Koita K., Morita K., Harabuchi Y., Kataura A., Hinoda Y. (1997) *"Diagnosis and Treatment of Malignant Lymphoma of the Parotid Gland"*, Japanese Journal of Clinical Oncology, vol. 28,issue 4, p.245.

46). Ho K., Lin H., Ann D. K., Chu P. G., Yen Y. (2011) *"An overview of the rare parotid gland cancer"*, Head & Neck Oncology, 3:40.

47). Horsburgh A., Massoud T. (2013) *"The salivary ducts of Wharton and Stenson: Analysis of normal variant sialographic morphometry and a historical review"*, Annals of Anatomy, Elsevier, 195, p.238-242.

48). Huang M.-W., Zhang J.-G., Zhang J., Liu S.-M., Zheng L., Shi Y., Shi D.-Y., Yu G.-Y. (2012) *"Oncocytic Carcinoma of the Parotid Gland"*, Laryngoscope, 123: 381-385.

49). Ibric-Cioranu V., Ibric-Cioranu S., Făgeţan I., Neacşu R., Petrescu Seceleanu V., Roman A., Rusu M. (2012) *"Chirurgie oro-maxilo-facială"*, Ed. Universităţii "Lucian Blaga"din Sibiu, Sibiu, p.154-159, 162-163.

50). Iguchi H., Yamane H. (2014) *"Pleomorphic Adenoma of the Accessory Parotid Gland"*, Austin Journal of Otolaryngology, vol. 1, issue 1.

51). Jaiswal A. A., Garg A. K., Membally R. (2014) *"Pleomorphic adenoma of parotid gland with extensive bone formation – A rare case report"*, Egiptian Journal of Ear, Nose, Throat and Allied Scences 15, 139-142.

52). Jaryszak E., Shah R., Bauman N., Howell R., Rossi C., Preciado D. (2011) *"Unexpected pathologies in pediatric parotid lesions: Management paradigms revisited"*, International Journal of Pediatric Otorhinolaryngology, Elsevier,75, p. 558-563.

53). Jung J., Cho J., Chae S., Lee H., Hwang S., Woo J. (2011) *"Epithelial Na+ channel (ENaC) expression in obstructive sialadenitis of submandibulary gland"*,Archives of Oral Biology 56,p.121-126.

54). Kanzhuly M. K., Gupta D. K., Muralidharan C. G. (2014) *"A Rare Case of Suppurative Parotitis with Facial Nerve Palsy"*, International Journal of Otolaryngology and Head & Neck Surgery, 3, 248-251.

55). Kasarskis E., Hodskins J., Clair W. (2011) *"Unilateral parotid electron beam radiotherapy as palliative*

treatment for sialorrhea in amyotrophic lateral sclerosis", Journal of the Neurological Science, Elsevier, 308, p.155-157.

56). Khanfour A., A., Metwally E. S. A. M. (2014) *"Marginal mandibular branch of the facial nerve: An anatomical study"*, Alexandria Journal of Medicine, 50, 131-138.

57). Kim D.-Y., Park G. C., Cho Y.-W., Choi S.-H. (2014) *"Partial Superficial Parotidectomy via Retroauricular Hairline Incision"*, Clinical and Experimental Otorhinolaryngology, vol. 7, no. 2: 119-122.

58). Konofaos P., Spartalis E., Katsaronis P., Kouraklis G. (2011) *"Primary Parotid Gland Lymphoma: a Case Report",* Journal of Medical Case Reports 5:38.

59). Lascar I., Zamfirescu D. (2000) *"Microchirurgie experimentală",* Ed. Paralela 45, București, p.92-105.

60). Lequerica-Fernandez P., Pena I., Villalain L., Rosado P., de Vincente J. C. (2011) *"Carcinoma of the parotid gland: developing prognostic indices"*, International Journal of Oral & Maxillofacial Surgery, 40, p. 821-828.

61). Li B., Zhang L., Zhao Z., Shen G., Wang X. (2013)*" Minimally invasive endoscopic resection of benign tumors of the accessory parotid gland: an updated approach"*, British Journal of Oral and Maxillofacial Surgery, Elsevier, 51, p. 342-346.

62). Lin D.,Jen Y., Lee J., Liu S.,Lin Y. (2011) *"Recurrence of nasopharyngeal carcinoma in the parotid region after parotid-gland-sparing radiotherapy"*, Journal of the Formosan Medical Association, Elsevier, 110, p.665-660.

63). Lore J. M.,Medina J.E. (2005) *"An Atlas of Head & Neck Surgery Fourth Edition"* Elsevier Saunders, Philadelphia.

64). Lupu G., Cristea B., Diaconescu B.,Stroică L. (2010) *"Anatomia omului cap și gât Lucrări practice"*, Ed. Universitară „Carol Davila" București.

65). Ma Q., Song H., Zhang P., Hou R., Cheng X., Lei D. (2010) *"Diagnosis and management of intraparotid facial nerve schwannoma"* Journal of Cranio-Maxillo-Facial Surgery 38, p. 271-273.

66). Mag A., Cotulbea S., Marin A., Doros C., Neamtu D., Balica N., Ruja A., Preda M. (2010) *"Carcinoma Ex-Pleomorphic Adenoma in Parotid Gland – Case Report",* Journal of Experimental Medical&Surgical Research, Timișoara, p.205.

67). Mandel L., Patel S., (2002) *"Sialadenosis Associated with Diabetes Mellitus: A Case Report"*, J. Oral Maxillofacial Surgery, 60, p.696-698.

68). Mandel L., Tomkoria (2000) "*Case Report- Differantiating HIV-1 Parotid Cysts from Papillary Cystadenoma Lymphamatosum",* JADA:772.

69).Marchesi M., Biffoni M., Trinchi S., Turriziani V., Campana F. P. (2006) *"Facial Nerve Function After Parotidectomy for Neoplasms with Deep Localization"*, Surgery Today, 36: 308-311.

70). Meadows A., Hall N., Shah-Desai S., Low J. L., Manners R. (2000) *"The House-Brackmann system and assessment of corneal risk in facial nerve palsy"*, Royal College of Ophthalmologists, 14, 353-357.

71). Micoiu E. M., Ibric Cioranu V., Neacșu R. I., Sabău D. (2014) *"Evoluția parezei postoperatorii de nerv facial după vitaminoterapie și acupunctură – prezentare de caz",*Acta Medica Transilvanica, Ed. Universității "Lucian Blaga" din Sibiu, 2 (3), p. 154-156.

72). Micoiu E. M., Ibric Cioranu V., Neacșu R. I., Sabău D. (2017) *"A Clinical Case of Spontaneous Mandibular Regrowth After Segmentary Resection and Follow-up of Inferior Alveolar and Cervico-Facial*

Nerves Recovery" Acta Medica Transilvanica, The Publishing House of "Lucian Blaga" University of Sibiu, 22 (2), p. 98-102.

73). Micoiu E. M., Neacşu R. I., Popenţiu A., Sabău D. (2016) *"The Evolution of the Post-Surgical Paresis of the Facial Nerve Under Treatment With Nimodipine in a Case of Madelung Disease"*, Acta Medica Transilvanica, The Publishing House of "Lucian Blaga" University of Sibiu, 21 (1), p. 78-81.

74). Micoiu E. M., Neacşu R. I., Sabău D. (2014) *"Evoluţia parezei postoperatorii a nervului facial după neurorafie şi vitaminoterapie într-un caz de tumoră Warthin gigantă"* Acta Medica Transilvanica, Ed. Universităţii "Lucian Blaga" din Sibiu, 2 (4), p. 53-55.

75). Miţariu M., Olinescu A. (2005) *"Imunologia mucoaselor şi cea oro-facială"*, Ed. Oastea Domnului, Sibiu, p. 103, 104, 123, 124.

76). Mommaerts M. Y., Murray E. F., Gundlach K.H. (2012) *" How to do clinical research in cranio-maxillo-facial surgery"*, Journal of Cranio-Maxillo-Facial Surgery 40, p.97-102.

77). Munir N., Tandom S., Brown J., Lesser T. (2012) *"Trans-mastoid facial nerve localization for malignant neoplasms confined to the parotid gland"*, British Journal of Oral and Maxillofacial Surgery, Elsevier, 50, p. 736-738.

78). Musani A., Zafar A., Suhail Z., Malik S., Mirza D. (2014) *"Facial Nerve Morbidity Following Surgery for Benign Parotid Tumors"*, Journal of the College of Physicians and Surgeons Pakistan, 24 (8): 569-572.

79). Narayanan V., Ramadorai A., Ravi P., Nirvikalpa N. (2012) *"Transmasseteric anterior parotid approach for condylar fractures: experience of 129 cases"*,British Journal of Oral and Maxillofacial Surgery, Elsevier, 50, p.420-424.

80). Neurovit Salvat în data de 25.08.2013 de pe adresa: http://www.farmacieonline. md/produs/neurovit-90mg-0-25mg-40-mg-n10x3.html-90-mg-0-25mg-40mg.

81). Orabona G. D. A., Abbate V., Piombino P., Romano A., Schonauer F., Iaconetta G., Salzano G., Farina F., Califano L. (2015) *"Warthin's tumor: Aetiopathogenesis dilemma, ten years of our experience"*, Journal of Cranio-Maxillo-Facial Surgery 43, 427-431.

82). Papilian V.(2003*) "Anatomia omului"* vol.II, Ed.BIC All, Bucureşti, p.49,51,52.

83). Papilian V., Roşca Gh. (1978) *"Tratat elementar de histologie"*, Ed. Dacia Cluj-Napoca, p.44-46.

84). Passos I. M., Massuda E. T., Hyppolito M.A., Colli B. O., Damico T. A. (2015) *"Rare case of neurinoma of the facial nerve"*, Brazilian Journal of Otorhinolaryngology, 81(2): 226-227.

85). Peng Z., Xu Z., Wen W., Wang R. (2011) *"Tea polyphenols protect against irradiation-induced injury in submandibular glands' cells: A preliminary study"*,Archives of Oral Biology, Elsevier, 56, p.738-743.

86). Pepper J., Kim J., Massry G. (2012) *"A surgical algorithm for lower eyelid resuspension in facial nerve paralysis"*, Operative Techniques in Otolaryngology, Elsevier, 23, p. 248-252.

87). Pleşca-Manea L., Blidaru M., Pîrvu A., Mîrza M., Strugar P. (1998) *"Manual de fiziopatologie generală pentru studenţii facultăţii de stomatologie an II"*, Tipografia U.M.F. Cluj-Napoca, Cluj-Napoca, p.99, 100.

88). Pons Y., Alves A., Clement P., Conessa C. (2012) *"Salivary duct carcinoma of the parotid"*, European Annals of Otorhinolaryngology, Head and Neck diseases, Elsevier Masson, 128, p. 194-196.

89). Popescu V., Banias L., Lazar Ş., Simu G., Popuţ C., Ciuce C., Irimie A. (1996) *"Chirurgia parotidei tumorale"*, Ed. Sincron, p. 62, 113-180.

90). Raica M., Caruntu I., Campean A., Suciu C. (2009) *"Histologia organelor Curs pentru studentii anului II*

Medicina generala", Lito UMF "Victor Babes" Timisoara, p. 111-112. 91). Rapids A., Givalos N., Gakiopulou H., Stavrianos S., Faratzis G., Lagogiannis G., Katsilieris I., Patsouris E.(2006) *"Mucoepidermoid Carcinoma of the Salivary Glands – Review of the Literature and Clinicopathological Analysis of 18 Patiens"*, Oral Oncology. 92). Raimondo S., Fornaro M., Tos P., Battiston B., Giacobini-Robecchi M., Geuna S. (2011) *"Perspectives in regeneration and tissue engineering of peripheral nerves"*, Annals of Anatomy, Elsevier, 193, p. 334-340.

93). Robinson M., Baiungo J., Hohman M., Hadlock T. (2012) *"Facial rehabilitation"*, Operative Techniques in Otolaryngology, Elsevier, 23,p. 288-296.

94). Rodrigues A., Andreo J., Menezes L., Chinellato T., Rosa Junior G. (2009) *"Anatomy of the Facial Nerve and its Implication in the Surgical Procedures"*, Int. J. Morphol., 27 (1): 183-186, 2009.

95). Rosen F., Bailey B. (2001) *"Anatomy and Physiology of the Salivary Glands, Source Grand Rounds Presentation"*, UTMB, Dpt. of Otolaryngology.

96). Roşca E., Coroi M., Drăgan A., Muțiu G., Roşca D. *"Aspecte histopatologice în carcinosarcom de glanda parotidă – studiu anatomopatologic pe un caz cu completarea datelor din literatură"*. Salvat in data de 30.07. 2012 de pe adresa: http://www.scritube.com/medicina/Aspecte-histopatologice-in-car93168php.

97). Roşca S. (1992) *"Histologie vol II Lucrări practice"*, Litografia Universității Sibiu, Sibiu, p.114,115.

98). Rosca S., Rosca Gh. (2000) *" Curs de histologie Vol. II Sisteme-Aparate"* , p. 8-11

99). Ruiz-Goday L., Suarez L., Mosqueda A., Meneses A. (2006) *"Polymorphous Low-grade Adenocarcinoma of the Parotid Gland Case Report and Review of the Literature"*, Med. Oral Patol. Cir. Bucal, 12:E30.

100). Rusu V., Chiriță V., Iliescu B., Gridinoc L., Naum G., Cirimbei R., Grigoriu D., Ignat B., Rusu T., Apetrei C., Bădescu L. (2001) *"Dicționar medical"*, Ed Medicală, București, p. 710.

101). Scheller K., Scheller C. (2012) *"Nimodipine promotes regeneration of peripheral facial nerve function after traumatic injury following maxillofacial surgery: An off label pilot-study"* Journal of Cranio-Maxillo-Facial Surgery 40, p.427-434.

102). Scutelnicu D. (2007) *" Elemente de semiologie neurologică Îndreptar pentru stagiu"*, Ed. Mirton, Timişoara, p.164.

103). Seres-Strum L., Niculescu V., Matusz (1997) *"Anatomie stomatologică și cervico-oro-facială"*, Ed. Mirton, Timişoara, p.117-129, 356, 553-560.

104). Sforza C., Guzzo M., Mapelli A., Ibba T. M.,Scaramellini G., Ferrario V. F. (2012) *"Facial mimicry after conservative parotidectomy: a three-dimensional optoelectronic study"*, International Journal of Oral & Maxillofacial Surgery, 41, p. 986-993.

105). Shrestha S., Gurung N. V., Upadhaya P.(2011) *"Superficial Parotidectomy: Comparison of Anterograde Versus Retrograde Facial Nerve Dissection"*, Postgraduate Medical Journal of NAMS, Vol. 11, Nr. 1, p. 38-40.

106). Sinelnikov R.D.(1976) *"Atlas de Anatomia Humana Tomo II Estudios de las Visceras y de los Vasos"* Ed. MIR, Moscu, URSS.

107). Singla N., Rathod G., Singla D. (2015) *"Adenoid cystic carcinoma of the parotid gland – A case report and review of literature"*,International Archives of Integrated Medicine, vol. 2, issue 4.

108). Sinopidis X., Fouzas S., Ginopoulou A., Pantiora A., Mantagos S., Papanastasiou D., Salakos C. (2011) *"Foreign body migration through the parotid duct causing suppurative parotitis"*, International Journal of Pediatric Otorhinolaryngology Extra 6, p. 87-88

109). Snell R. S., Kluwer W. (2004) *"Clinical Anatomy By Regions, Eighth Edition"* Lippincott Williams&Wilkins, Philadelphia,SUA.

110). Sodhi K., Bartlett M., Prabhu N.(2011) *"Role of high resolution ultrasound in parotid lesions in children"*,International Journal of Pediatric Otorhinolaryngology, Elsevier,75, p.1353-1358.

111). Spence A. P.,Mason E. B. (1987) *"Human Anatomy and Physiology Third Edition"* The Benjamin/ Cumming Publishing Company. Inc California

112). Stenner M., Demgensky A., Molls C., Hardt A., Luers J., Grosheva M., Huebbers C., Klussmann J. (2011) *"Prognostic value of surviving expression in parotid gland cancer in consideration of different histological subtypes"*, European Journal of Cancer, Elsevier, 47, p. 1013-1020.

113). Standring S., Anand N., Birch R., Collins P., Crossman A., Gleeson M., Jawaheer G., Smith A., Spratt J., Stringer M., Tubbs R., Tunstall R., Wein A., Wigley C. (2016) *"Gray's anatomy: The Anatomical Basis of Clinical Practice"*, p. 502, 503.

114). Sujeeth S., Dindawar S. (2011) *"Parotid duct repair using an epidural catheter"*, Int. J. Oral Maxillofac. Surg., Elsevier, 40, p.747-748.

115). Tan S., Staino J., Itinteang T., McIntyre B., MacKinnon C., Glasson D. (2012) *"Gold weight implantation and lateral tarsorrhaphy for upper eyelid paralysis"*, Journal of Cranio-Maxillo-Facial Surgery, Elsevier, p.1-5.

116).Tillmann Bernhard N., Sperlich C., Franke C., Cornford A. (2005) *"Atlas der Anatomie des Menschen"* Ed.Springer, Berlin.

117). Trandafir D., Gogalniceanu D., Trandafir V., Vicol, Costan V. (2007) *"Lipoamele: Tumori rare ale glandei parotide"*, Jurnalul de Chirurgie, Iaşi, vol. 3, nr.2, p.156.

118). Veen G., Giltay E., Vreeburg S., Licht C., Cobbaert C.,Zitman F., Pennix B. (2012) *"Determinants of salivary evening alpha-amylase in a large sample of psychopathology"*,International Journal of Psychophysiology, Elsevier,84, p. 33-38.

119). Vidic B.(Editorii ediţiei româneşti: Seres-Strum L., Solomon L. B.) (2001) *"Anatomia omului Atlas fotografic"* Ed. Mosby , Ed. Medicală, Bucureşti .

120). Voiculescu M., Angelescu M., Căruntu V., Chiotan M., Dancu I., Dediu Şt., Leonescu M., Păun L., Perederi S., Predescu I., Rebedea I., Taindel Cl., Valeriu A., Zamfirescu I. (1976) *"Boli infecţioase"*, Ed. Didactică şi Pedagogică, Bucureşti, p.175.

121). Wang X., Luo E., Li Y., Hu J. (2011) *"Schwann-like mesenchymal stem cells within vein graft facilitate facial nerve regeneration and remyelination"*, Brain Research 1383, Elsevier, p.71-80.

122). Wheater P., Burkitt H., Daniels V. (1987) *"Functional Histology a Text and Colour Atlas"*, Churchill Livingstone, Edinburg, London, Melbourne, New York, p. 200-201.

123). Yadav J., Chouhan M., Mody R., Bakhsi J. (2011) *" Heamangioma of submandibular gland - A rare entity"*, International Journal of Pediatric Otorhinolaryngology Extra 6, Elsevier, p. 189-191.

124). Yilmaz M., Akil F., Yener H. M., Aydin F., Acar G.O., Enver O. (2013) *"Submandibular Gland Excision: 10 – Year Outcome"*, Otolaryngology , 3:3.

125). Yuce S., Uysal I. O., Dogan M., Karakus C. F.,Polat K., Muderris S. (2013) *"Surgical treatment of parotid gland pleomorphic adenomas: Our experiments and literature review"*, Global Advanced Research Journal of Medicine and Medical Sciences vol. 2 p. 125-127.

126). ''*Teste statistice parametrice de comparare*'' Salvat în data de 22.04.2018 de pe adresa: http://www.scritub.com/stiinta/matematica/Teste-statistice-parametrice-d6431101.php