GRIGORE T. POPA UNIVERSITY OF
MEDICINE AND PHARMACY IASI

HABILITATION THESIS

Insights into Oral and Maxillofacial Surgery: From Practice to Research

Victor Vlad Costan,

Associate Professor, MD, DMD, PhD

2020

CONTENTS

ABSTRACT

The habilitation thesis entitled “Insights into Oral and Maxillofacial Surgery: From Practice to Research” provides an overview of my professional, academic and scientific contributions from the postdoctoral period to the current status. It focuses mainly on three subjects of research that comprise different aspects of surgical practice, from the complex surgery of the orbital and periorbital regions to minimally invasive techniques in the area of reconstructive surgery using autologous fat grafting, as well as minimally invasive procedures used in salivary gland pathology. Areas of scientific interest and future development are also highlighted.

The thesis was elaborated in accordance with the recommendations of The National Council for the Attestation of University Titles, Diplomas and Certificates (CNATDCU), according to the Order of the Ministry of Education and Scientific Research no 3121/2015. It is divided in three main sections, starting with an overview of the professional, academic and scientific developments, underlining the personal contribution in the field of oral and maxillofacial surgery, followed by the projects for future professional and scientific development, as well as a full list of relevant bibliographic references in the national and international context of knowledge regarding the approached research domain.

The first section is structured in three chapters. An overview of my professional, academic, and scientific activity to the present time is presented in the introduction. Within each chapter, the most relevant publications in the area of the discussed pathology are mentioned.

The first chapter - “Clinical and surgical approaches in orbital pathology” underlines the challenging management of different disorders involving the orbit, an anatomical region located at the crossroads of multiple medical and surgical specialties. The chapter is structured in five subchapters focusing on different aspects of orbital pathology, from the general presentation of the surgical management of orbital and periorbital conditions, to presenting our experience regarding the management of autoimmune, vascular and tumor orbital pathology, as well as regarding the reconstruction of complex defects involving the orbit.

The second chapter - “Adipose tissue in oral and maxillofacial surgery” is structured into four subchapters presenting the current existing concepts on autologous fat grafting in head and neck reconstruction, followed by the results we achieved using this technique for the rehabilitation of regions with particular reconstructive requirements- the periocular region and the oral and perioral regions, as well as our experience with autologous fat grafting in the reconstruction of defects following oncologic surgery.

The third chapter - “Minimally invasive clinical and surgical approaches in salivary gland pathology” contains four subchapters, the first one focusing on the general presentation of minimally invasive procedures used in the management of different salivary gland disorders and their role in achieving improved appearance and function. The other three subchapters present our experience on using specific minimally invasive techniques aimed at avoiding the complications and addressing the sequelae associated with classic salivary gland procedures.

The second section is dedicated to projects of evolution and future development regarding research and career activity. The first subsection underlines the main future research directions, represented by the reconstruction of extended defects in the maxillofacial territory using epitheses or microvascular free flaps, as well as implementing three-dimensional printing in various aspects of clinical practice, and developing additional benefits of previously approached research subjects, such as autologous fat transfer. The second subsection refers to the future directions in teaching activity with students, residents and doctoral students. The third subsection mentions directions for future professional activity.

The third section contains a list of relevant bibliographic references in the context of contemporary knowledge regarding the approached subjects.

REZUMAT

Teza de abilitare intitulată "Perspective în chirurgia orală și maxilo-facială: de la practică la cercetare" oferă o imagine de ansamblu asupra contribuțiilor mele profesionale, academice și științifice din perioada postdoctorală până la momentul actual. Este axată în principal pe trei direcții de cercetare, ce abordează aspecte diferite ale practicii chirurgicale, de la chirurgia complexă a regiunii orbitare și periorbitare, la tehnici minim invazive, cum este grefa autologă de grăsime utilizată în cadrul procedurilor reconstructive, dar și alte proceduri minim invazive utilizate în patologia glandelor salivare. De asemenea, sunt descrise în teză și domeniile de interes științific și de dezvoltare viitoare.

Teza a fost elaborată în conformitate cu recomandările Consiliului Național pentru Atestarea Titlurilor, Diplomelor și Certificatelor Universitare (CNATDCU), conform ordinului Ministerului Educației și Cercetării Științifice nr. 3121/2015. Este structurată în trei secțiuni principale, începând cu o prezentare generală a evoluției profesionale, academice și științifice, cu sublinierea contribuțiilor personale în domeniul chirurgiei orale și maxilo-faciale, urmând descrierea proiectelor de dezvoltare profesională și științifică viitoare, iar ulterior prezentând lista completă a referințelor bibliografice relevante în contextul cunoașterii naționale și internaționale în domeniul cercetării abordate.

Prima secțiune cuprinde trei capitole. În introducere este expusă o prezentare generală a activității proprii profesionale, academice și științifice, până la momentul actual. În cadrul fiecărui capitol sunt menționate cele mai relevante publicații din domeniul patologiei prezentate.

Primul capitol – „Abordarea clinică și chirurgicală a patologiei orbitare” subliniază dificultățile de management în diferite afecțiuni ale orbitei, aceasta fiind o zonă anatomică aflată la intersecția dintre multiple specialități medicale și chirurgicale. Capitolul cuprinde cinci subcapitole axate pe aspecte diferite ale patologiei orbitare, de la prezentarea generală a modalităților de abordare chirurgicală a afecțiunilor orbitare și peri-orbitare, pană la expunerea experienței proprii privind managementul patologiei orbitare autoimune, vasculare și tumorale, dar și al reconstrucției defectelor complexe implicând orbita.

Al doilea capitol – „Utilizarea țesutului adipos în chirurgia orală și maxilo-facială” este structurat în patru subcapitole ce prezintă conceptele actuale privind transferul de țesut adipos ca procedură reconstructivă în teritoriul capului și al gâtului, urmând prezentarea rezultatelor proprii obținute prin utilizarea acestei tehnici. Este prezentată atât experiența în reabilitarea unor regiuni cu caracteristici reconstructive particulare, regiunea peri-oculară și regiunile orală și peri-orală, cât și cea rezultată din utilizarea grefei autologe de grăsime în reconstrucția unor defecte consecutive chirurgiei oncologice.

Al treilea capitol – „Abordarea clinică și chirurgicală minim invazivă a patologiei glandelor salivare” cuprinde patru subcapitole. Primul este axat pe prezentarea generală a procedurilor minim invazive utilizate în managementul diferitelor afecțiuni ale glandelor salivare și evidențierea rolului acestora în îmbunătățirea rezultatelor sub aspect funcțional și estetic. Următoarele trei subcapitole prezintă experiența proprie privind utilizarea unor proceduri minim invazive specifice în vederea evitării complicațiilor și a reducerii sechelelor asociate cu procedurile chirurgicale clasice utilizate în patologia glandelor salivare.

Cea de-a doua secțiune este dedicată proiectelor de evoluție și dezvoltare viitoare, privind activitatea de cercetare și cariera medicală. Prima subsecțiune subliniază principalele direcții de cercetare, reprezentate de reconstrucția defectelor extinse din teritoriul oro-maxilo-facial cu ajutorul epitezelor sau al lambourilor libere microvasculare, dar şi privind utilizarea modelelor stereolitice imprimate tridimensional în diferite aspecte ale practicii clinice, precum și dezvoltarea unor aspecte adiționale ale unor subiecte de cercetare abordate anterior, cum ar fi grefa autologă de grăsime. A doua subsecțiune se referă la direcțiile de dezvoltare privind activitatea didactică cu studenții, medicii rezidenți și studenții doctoranzi. A treia subsecțiune menționează planurile de dezvoltare a activității profesionale.

A treia secțiune cuprinde o listă de referințe bibliografice, relevante în contextul cunoașterii actuale privind subiectele abordate.

SECTION I

OVERVIEW OF PROFESSIONAL, ACADEMIC AND SCIENTIFIC ACTIVITY

The habilitation thesis entitled “Insights into Oral and Maxillofacial Surgery: From Practice to Research” summarizes my research activity following the graduation of my PhD thesis entitled “The value of the pedicled fascial temporo-parietal flap in the reconstruction of substance loss in the OMF territory” under the coordination of Prof. Dr. Dan Gogălniceanu, confirmed by order of the Ministry of Education, Research and Youth (no 5837/04.11.2008, Diploma F Nr. 0011663).

In my doctorate thesis I focused on refining the results achieved in the reconstruction of various defects in the maxillofacial territory, including defects in the periorbital region, by using the versatile temporo-parietal flap. In the last ten years I continued to develop multiple reconstructive techniques suitable for defects of various sizes, thickness, composition, and locations, with particular interest in the anatomically complex orbital and periorbital region. In this attempt, it was imperative to develop multidisciplinary teams in both clinical practice and research, since this region comprises a great density of anatomical structures found at the convergence point of multiple specialties, requiring a combined approach to the diagnosis, treatment and follow-up for achieving the best outcomes.

Currently, I am associate professor in the Oral and Maxillofacial Discipline, Surgery Department, of the Faculty of Dental Medicine of the Grigore T. Popa University of Medicine and Pharmacy from Iasi, with twenty years of experience in the academic field. I also work as a senior physician in the Oral and Maxillofacial Clinic of the St. Spiridon Emergency Hospital form Iasi. Both my professional and academic activity are in the field of maxillofacial surgery and represent the infrastructure of the present research. I do my best to reconcile and to continuously improve all aspects of my current activity in order to contribute to and reimburse general progress in the medical and academic fields.

Professional activity

My passion for reconstructive surgery began as a medical student, twenty-four years ago, during summer practice in plastic surgery performed during several years in Iasi, Piatra Neamt and in Villingen-Schwenningen, Germany. After graduating medical school in 1997, and internship in 1999, I succeeded in becoming an oral and maxillofacial surgery resident in the year 2000. Of the total five years of residency training, two were spent practicing in the Centre Hospitalier Roanne - Dr. Yves Le Bescond, Roanne, France. During this time, I obtained a master’s degree in microsurgical techniques, at the University Claude Bernard, Lyon. I completed training in Dental Medicine in 2002. In 2005 I became a specialist doctor in maxillofacial surgery, and then a primary physician in 2009.

As a member in several societies of Oral and Maxillofacial surgery, both national and international, I have constantly participated in conferences and courses that helped me select and develop surgical techniques, but also set helpful collaborations with surgeons in different locations. This allowed important exchange in experience and information that manifested in gradual positive changes in clinical practice and research. Some of the techniques that I focused on and continued to develop so far during my professional activity are orbital decompression surgery, structural fat grafting, flap surgery and microsurgical reconstruction.

Academic activity

I started my journey in the academic field in the year 2000 as a Junior Teaching Assistant in the discipline of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi. I then gradually progressed to University Assistant in 2003, Lecturer in the year 2012 and Associate Professor in 2019.

In the beginnings of my career, my teaching and professional skills were developed under the guidance of experienced professors in oral and maxillofacial surgery. I continued to expand the teaching methods used by undergoing a psycho-pedagogy course, which I graduated in 2005. This allowed me to better adapt and individualize teaching to the needs of each student, as well as designing more interactive and captivating classes. The integration of clinical photography in my professional activity supplied enough documented materials for the gradual development of original visually rich slides that illustrate most of the study subjects in the curricula.

Since the beginning of my teaching career as a lecturer, I held courses of Oral and Maxillofacial Surgery for dental medicine students in the 5th and 6th year from the English and French sections, for the 5th year dental medicine students of the Romanian section, as well as courses of Cranio-Maxillofacial Surgery for general medicine students in the 6th year from the Romanian, English and French sections. Additionally, I held Oral and Maxillofacial Surgery courses for students in the 3rd year of College of Dental Technology.

I focused on presenting the students updated information on the study subjects, by continuously adapting and improving the course materials with the newest research and developments in the field. Regular participation in national, European, and International conferences allowed me to stay up to date with novelties in the field of maxillofacial surgery and related topics, which also translated in developing subjects for research. The practical aspect of the taught issues was another priority and multiple presentations of clinical cases were used for exemplification. Communication with students was encouraged in order to better understand their needs and to resolve existing issues. I particularly encouraged argumentation as a means of better understanding all aspects of the taught topic.

I encouraged students in participating in clinical, academic and research activities. In this regard, I have guided 38 license theses for dental medicine and general medicine students from the Romanian, English, and French sections. I promoted and guided the active participation of students in scientific student manifestations and workshops. I also guided the practical and theoretical training of residents in Oral and Maxillofacial Surgery and endorsed them in engaging in research projects and academic careers.

I contributed to increasing the visibility of the University by participating with oral presentations and poster presentations in national and international conferences held on the topic of maxillofacial surgery, but also related topics like orthodontics, endocrinology, otolaryngology, plastic surgery, ophthalmology and oncology.

Research activity

In 2008 I obtained my PhD diploma for the doctoral thesis entitled “The value of the pedicled fascial temporo-parietal flap in the reconstruction of substance loss in the OMF territory” under the coordination of Prof. Dr. Dan Gogălniceanu. The results achieved in my dissertation thesis were later published as a monograph “The use of the superficial temporal artery in oral and maxillofacial surgery”, in 2010, at the “Gr. T. Popa” UMF Iași Publishing House.

In 2016 I edited a book for an internationally acknowledged Publishing House-Springer, a monograph entitled “Management of Extended Parotid Tumors”, in which I also coauthored 12 chapters.

I published 60 ISI indexed publications, of which 18 ISI rated manuscripts as a main author and 6 as a coauthor. I also authored 67 BDI indexed publications, of which 46 as a main author and 21 as coauthor. The impact of the research work is outlined by the 203 citations in Web of Science Core Collection, of which 157 without self-citations, with a h-index of 9 according to Clarivate Analytics Web of Science Core Collection.

I am a member in nine scientific and professional societies, including the Romanian, European (EACMFS) and International (IAOMS) associations of maxillofacial surgery. Between the year 2000 and 2018, I participated in over 100 local, national, and international scientific manifestations including courses, congresses, conferences, and symposiums. I was a lector in six national and international scientific manifestations, a chairman in two international conferences on oncology and maxillofacial surgery held in Barcelona (21st ICOMS, 2013) and Hong Kong (23rd ICOMS, 2017). Additionally, I was a member in the organizing committee of two international congresses held in Bucharest (20th BaSS Congress 2015) and Iasi (9th International ADRE Congress, 2017).

I was a team member in two national grants won by competition, regarding the use of information technologies for learning and improving imaging diagnosis in maxillofacial pathology (Grant CNCSIS nr. AI/GR 162/16.05.2006, Grant director Prof. Dr. Danisia Haba), and the antitumor role of vitamin D in patients with head and neck cancer (Grant CNCSIS nr. 6/GR/16.05.2006, Grant director Conf. Dr. Veronica Mocanu).

CHAPTER 1.
CLINICAL AND SURGICAL APPROACHES IN ORBITAL PATHOLOGY

1.1. STATE OF THE ART IN ORBITAL AND PERIORBITAL SURGERY

The particularity of the orbital region resides in the great anatomical complexity and density of delicate structures that function in interrelation in order to ensure optimal visual function. Nevertheless, this region also plays a compelling role in facial appearance and social interactions (Fay, Dolman, 2017). Any disbalance in the structure or functioning of the composing elements, either due to an existing disorder or trauma, including surgical trauma, may lead to modifications altering the visual function, with important repercussions in performing everyday activities and profession. Appearance change is an important aspect, regarding both self-image and the perception of other people, that may limit social activities and further decrease the quality of life of the patient (Campbell et al.,2015; Chambers, Moe, 2017).

Orbital surgery is especially problematic, since any incision and dissection in this region will result in some degree of scarring, with various effects on the mobile tissues in the orbital and periorbital area. The presence of delicate structures like the globe, optic nerve and the skull base in direct proximity, further complicates surgery. In this regard, the best suited approach to orbital pathology diagnosis, treatment and follow-up should involve multiple specialties in order to achieve the most benefit regarding form and function (Markiewicz, Bell, 2012; Fay, Dolman, 2017).

1.1.1. Approaches to the orbit

"Round-the-Clock" surgical approaches to the orbit have been described (Paluzzi et al., 2015). Considering the purpose of orbital access, multiple techniques exist, varying from simple to complex and from non-invasive to invasive. The development of new technology, such as endoscopic approaches, navigation surgery and three-dimensional stereolithic model planning, allows the surgeon to select the least invasive approach that still provides adequate access for the defined goal (Campbell et al., 2015). Extended approaches are useful for tumor surgery, especially for extended tumors, when there is need in accessing the lateral or anterior skull base, the infratemporal fossa or paranasal sinuses. Less invasive and minimally invasive approaches are used for trauma surgery or benign tumor ablation. With proper indication and technique, or by association of various approaches, they can provide sufficient exposure for the majority of orbital pathology.

The transconjunctival approach is maybe the most popular minimally invasive route to the orbit since it provides enough access for the entire orbital floor with possibility for modifications. The exposure can be extended by performing a transcaruncular incision to access the medial orbital wall, or a lateral canthal incision for access to the lateral orbit. Different level inferior palpebral incisions are also extensively used since the scars are well hidden in natural skin folds. Concerns of postoperative inferior eyelid ectropion determine many surgeons to opt for the transconjunctival approach instead of the inferior eyelid, especially avoiding the subcilliary incision, whenever possible. The superior eyelid blepharoplasty incision, as well as the brow incision are useful in reaching the superior-lateral orbital rim (Markiewicz, Bell, 2012). The classical Lynch incision, a curvilinear incision located midway between the internal canthal region and the nasal dorsum, used for access to the medial orbit, is not commonly used due to the increased visibility of the postoperative scar and the frailty of the local soft tissues that encourage the onset of complications (Markiewicz, Bell, 2012).

The transnasal endoscopic route provides access to the medial orbit, inferior orbital floor, paranasal sinuses and skull base. This approach may be suitable as a less invasive route for removal of deeply located benign tumors involving the orbit and paranasal sinuses, with possible extension to the anterior skull base (Yao et al., 2016; Kong et al., 2018). Navigation surgery and intraoperative imaging increase the precision of endoscopic procedures, or even classical procedures, especially when accessing narrow spaces that host vital structures that must be protected during surgery, such as the optic nerve, dura mater, brain tissue, internal carotid artery. The use of stereolithic models for preoperative planning allows a preview of the patient’s anatomy and increased confidence in accessing difficult regions. Additionally, the possibility of modelling the reconstructive material in advance, allows the use of less extensive approaches for the insertion and fixation of the material, especially in trauma cases or reconstruction procedures following the removal of benign tumors (Susarla et al., 2015; Herford et al., 2017; Jansen et al., 2018).

Surgery for the ablation of malignant tumors involving the orbit and paranasal sinuses may necessitate additional access, such as the Weber-Ferguson or Nelaton approaches. The transantral route is another way of accessing the orbital floor, often in association with the previous incisions (Paluzzi et al., 2015; Yao et al., 2016).

An invasive classic technique to reach the orbit is the coronal approach for access to the lateral, superior and medial orbit, as well as the zygomatic arch and infratemporal fossa. A zygomatic bone osteotomy facilitates access to the infratemporal fossa (Markiewicz, Bell, 2012). The transfrontal route used in conjunction with the coronal approach, allows superior access to the orbital apex and anterior skull base. A lateral orbitotomy can be performed through a curved incision following a line from the pretragian region to the midline superior aspect of the anterior hairline, called “widow’s peak incision”. It can be modified into a coronal-type incision in case of need. These invasive approaches are most often used for the removal of extended malignant tumors and necessitate multidisciplinary teams in cases of intracranial extension (Markiewicz, Bell, 2012; Jansen et al., 2018).

1.1.2. Surgery for Graves’ ophthalmopathy

Graves’ ophthalmopathy is characterized by mechanical changes in the orbital tissues, including proptosis, due to the increased orbital pressure caused by an augmented orbital volume consisting of enlarged fat compartment, muscle compartment, or lacrimal gland, in the context of the known chronic autoimmune multisystemic disorder (Kotwal, Stan, 2018; Tieghi et al., 2010).

Thyroid eye disease is mostly managed medically, aiming for stabilization of the disease. Cases that are unresponsive to medical treatment may benefit from orbital decompression surgery, as well as vision threatening emergencies involving optic neuropathy. It is estimated that one out of 20 patients with Graves’ orbitopathy will necessitate decompression surgery in the first year following diagnostic, while four out of 20 patients will have surgery in the initial ten years (Victores, Takashima, 2016). The goal of surgery is to prevent vision loss, improve diplopia, achieve good corneal coverage and improve facial appearance.

Surgical procedures for Graves’ ophthalmopathy include orbital decompression, strabismus surgery and blepharoplasty, usually performed in this order, since the tissue modifications that follow each procedure may change the indication for further surgery. The preferences regarding the type of orbital decompression performed are different according to the characteristics of each individual case and the experience of the surgeon (Rootman, 2018).

Orbital decompression surgery is in effect the remodeling of the orbital soft tissues and bone frame in order to adjust the volume, or to redistribute it, for achieving an optimal level of the eyes, prevent the compression of the orbital apex region, mainly the optic nerve, and preserve function, including a normal range of eye movements. Options include variations on orbital fat decompression, bony wall decompression involving the complete or partial removal of one or several orbital walls, as well as variations regarding the approach used for access (Siracuse-Lee, Kazim, 2002; Wang et al., 2018).

An isolated fat decompression may be efficient in mild proptosis cases when imaging has found a prevalent increase in orbital fat. The removal of orbital adipose tissue has been stated to decrease the amount of proptosis by 2 to 4 mm, especially in the ophthalmopathy cases where the orbital fat is predominantly enlarged, as opposed to prevailing extraocular muscle hypertrophy (Braun et al., 2017). When pure orbital fat decompression is performed, it is recommended that both the extraconal and the intraconal fat should be removed, since it is the increased volume of the intraconal fat at the orbital apex that is incriminated in optic nerve compression and neuropathy (Imburgia et al., 2016; Tieghi et al., 2010). Additionally, some authors have advocated the removal of more fat from the inferior orbit, especially from the lateral part, due to the unequal anatomical distribution of the orbital adipose tissue (Rootman, 2018).

The increase in volume of the extraocular muscles seems to occur more frequently than pure fat increment. For this reason, most surgeons found good results by a combined orbital fat and wall decompression. The extent of bone wall removal is dependent on the degree of proptosis. All the orbital walls may be involved by surgery, but the preference for removing certain walls and associations of several walls, takes into consideration the complexity of the approach, the possible complications and the desired effect on the protrusion of the globe. The inferior orbital wall may be accessed via an incision in the inferior eyelid, through a transconjunctival approach, or transantral. Classically, a Lynch incision, or a coronal approach were used for reaching the medial orbit, but nowadays, the transcaruncular approach is mainly used for accessing the medial orbital wall. The transnasal endoscopic approach to the medial orbital wall and floor is another option (Wehrmann, Antisdel, 2017). A lateral canthotomy or a superior eyelid crease incision can be performed for reaching the lateral orbital wall. A more elaborated approach is usually necessary for the superolateral orbit, a transfrontal access via a coronal incision. This wall is rarely accessed as part of a four-wall decompression procedure, indicated only in severe cases, since it can reduce proptosis with up to 10 mm (Rootman, 2018). One study revealed a reduction of approximately 5 mm average in globe protrusion using the two-wall approach, and of 7 mm with the three-wall technique (Korkmaz, Konuk, 2016). In cases of moderate proptosis, a very useful procedure in the opinion of several authors (Park et al., 2015; Rootman, 2018; Jefferis et al., 2018) is a two-wall or one and a half wall decompression with fat decompression.

After the reduction of proptosis, other surgical procedures may be necessary for achieving good palpebral closure and corneal coverage. Upper eyelid retraction may be resolved by blepharoplasty, levator palpebrae aponeurosis recession, or botulinum toxin injections. Strabismus surgery is sometimes necessary for resolving imbalances in ocular movements due to unequal hypertrophy of the extraocular muscles, or even for complications following orbital decompression surgery with formation of scar tissue or injury to the extraocular muscles (Wu et al., 2017).

With adequate indication, the overall quality of life of patients with Graves' ophthalmopathy significantly improves after surgery (Wickwar et al., 2015). This is due to an improvement in facial appearance, but also the disappearance of diplopia and disturbing symptoms related to upper eyelid retraction.

1.1.3. The management of vascular lesions of the orbit

Vascular lesions developing inside the orbital cavity are sometimes diagnosed incidentally, before the appearance of clinical manifestations, as a result of imaging studies performed for a different pathology. In other instances, they are discovered during imaging investigations performed for unilateral progressive proptosis or for the presence of changes in vision, including diplopia (Bachelet et al., 2018). The early diagnosis of such space occupying orbital masses is crucial for ensuring functional rehabilitation, particularly regarding vision.

Cavernous hemangiomas are the most common vascular lesions of the orbit, accounting for approximately 4% of all orbital tumors (Clarós et al., 2019). They may develop unnoticed for a variable period, then they gradually become symptomatic due to their slow progressive growth, displacing the orbital contents and eventually causing compression on important anatomical structures, particularly the optic nerve. They preferentially develop in the intraconal space, causing axial proptosis (Calandriello et al., 2017). Spontaneous bleeding is rare but may cause vision loss due to the sudden compressive intraorbital hematoma development (Bachelet et al., 2018; Hegde et al., 2019).

The surgical treatment of orbital cavernous hemangiomas appears intimidating, considering the possible complications regarding the difficult hemostasis and potential optic nerve injury. Despite such concerns, their surgical removal can usually be performed safely, with rare complications, due to the relatively small caliber vessels present in the enclosed orbital space and due to the presence of a fibrous capsule delimiting the lesion from the surrounding orbital contents (Bachelet et al., 2018).

The approach for tumor removal is selected according to the size of the hemangioma, its location and extension within the orbit and adjacent anatomical structures (Calandriello et al., 2017). Although transnasal endoscopic approaches have been used for the removal of orbital hemangiomas, especially for those located medially to the optic nerve (Ma et al., 2019), open access surgery is still the preferred technique among many surgeons (Clarós et al., 2019).

Large intraorbital tumors may require an external lateral orbitotomy approach for safe removal, or even a transcranial approach depending on their characteristics (Hegde et al., 2019). Blunt, finger dissection within external approaches allows minimal manipulation of the hemangioma and adequate separation of tissues around the fibrous capsule (Bagheri et al., 2018). Although lateral orbitotomy was classically used for access in the majority of intraconal lesions, it is associated with unpleasant sequelae related to the extensive soft tissue dissection and particularly the difficulty of reconstructing the lateral bony wall of the orbit (Calandriello et al., 2017). Thus, minimally invasive approaches should be employed whenever possible (Kiratli et al., 2005).

Many authors underline the benefits of using the transconjunctival approach, which ensures an adequate access for most orbital cavernous hemangiomas and results in inconspicuous scars with optimal aesthetic outcomes and minimal overall complications (Kiratli et al., 2005; Cho et al., 2010; Davies et al., 2014; Sa et al., 2017). The complete separation of cavernous hemangiomas from the surrounding soft tissues by using a minimally invasive access is possible due to the fibrous capsule surrounding the mass, which creates a safe and easy dissection plane even in the confined space of the orbit (Cho et al., 2010). The surgery time is shortened using this approach and minimal tissue damage is ensued, in comparison to classical approaches involving bone removal and extensive soft tissue dissection as part of complex time-consuming techniques (Kiratli et al., 2005).

With careful selection of the least invasive access and dissection technique, cavernous hemangiomas of the orbit can be surgically removed with optimal outcomes regarding appearance and function (Calandriello et al., 2017; Sa et al., 2017).

1.1.4. Resection surgery for malignant tumors involving the orbit

The orbit and periorbital region host a considerable variety of tumor types. There is a great density of distinct tissues that compose the contents of the orbit, including bone, muscles, fat, vessels, sensory and motor nerves, connective tissue, glandular tissue, resulting in the possible development of various benign, malignant and inflammatory tumors with this location. In addition, neoplasms arising in neighboring structures including the paranasal sinuses and brain tissue, may extend to involve the orbit (Fay, Dolman, 2017).

Tumors with orbital invasion raise concerns regarding the maintenance of visual function and appearance, while achieving complete tumor resection with minimal surgery related complications. The shape of the orbit, the density of its composing elements and the proximity of vital structures, make resection surgery in this region particularly difficult. Adequate access and a proper technique ensuring functional preservation and a low complication rate are especially important in surgery performed for benign orbital tumors (Campbell et al., 2015; Hoffman et al., 2016).

The most challenging aspect of malignancies invading the orbit is the indication for performing orbital exenteration, since it is a debilitating procedure that is difficult to accept by patients. Biopsy should be performed before surgery for the removal of an orbital tumor in all cases but deciding type of biopsy is not always easy due to the deep location of the tumors and the difficult access. The presence of an intraorbital malignant tumor is an indication for performing an orbital exenteration in the majority of cases. When imaging studies are suggestive for intraorbital malignancy, one should not neglect the possible occurrence of rare tumors that do not have a clear indication for initial surgical treatment, such as the orbital lymphoma or sarcoma. For this reason, and additional concerns related to signed consent for orbital exenteration, a certain histopathology result should be obtained by performing biopsy prior to surgery (Sokoya et al., 2019).

The pattern of regional tumor spread is in relation with the anatomical planes that act either as barriers or gates for tumor invasion into adjacent structures. Regarding the extension of regional malignancies to the orbit, it is the periorbita that plays a crucial role in deciding the extent of surgical resection, as the last tissue barrier to tumor spread before the trespassing of the tumor cells into the orbital fat (Neel et al, 2017). Once the malignant tumor has surpassed the bony wall and breached the orbital periosteum, oncological safety with clear margins is difficult to achieve in the soft orbital fat and therefore, orbital exenteration is indicated for tumor control. Regional nodal metastases may occur in the parotid and cervical lymph nodes and raise concern for performing prophylactic or curative neck dissection, depending on the staging, associated risk factors and especially the histology of the tumor (Meads, Greenway, 2006; Nassab et al., 2007; Neel et al, 2017).

1.1.5. Reconstructive orbital and periorbital surgery

Trauma or surgery involving the orbit and surrounding tissues may lead to fibrotic changes and distortion of the local tissues, changes in soft tissue volume, absence of bone support, malpositions of the regional anatomical structures, or substance loss involving soft tissue, bone or composed defects (Chambers, Moe, 2017). Functional impairment may accompany any of the previously described modifications, in conjunction to cosmetic impairment. The goal of reconstructive surgery is to restore the lost function and appearance for improving the quality of life of the patient (Badhey et al., 2019).

Orbital reconstruction in the acute trauma setting involves the restoration of the orbital rims' contour and the continuity of the orbital walls, using titanium plates and titanium mesh. Other materials are available for the reconstruction of the orbital floor (Avashia et al., 2012), such as Dacron, polydioxanone (PDS), porous polyethylene, but titanium mesh is generally preferred due to its characteristics regarding biocompatibility, strength, malleability and configuration allowing drainage. Bone grafts may be used for extensive defects, but they are mainly indicated in the correction of sequalae following orbito-zygomatic fractures, sometimes in association with titanium mesh. The correction of posttraumatic sequelae in the orbital region is difficult to achieve due to the scarring and contraction of the soft tissues in addition to the modification of the bone support. Repositioning osteotomies may be necessary, together with bone grafts or implant materials, as well as soft tissue augmentation procedures like autologous fat grafting or silicone implant placement. Often, multiple procedures are required for reaching the desired outcome regarding form and function (Dubois et al., 2016).

In establishing the optimal method of orbital reconstruction following tumor surgery, one should have a clear vision of the purpose and desired outcomes of the surgery, as well as an understanding of defect extent and composition. In addition, an assessment of the local, regional, and distant tissues available for reconstruction must be performed since the gold standard is replacing like with like. This desiderate is especially difficult in the orbital region due to the presence of a very thin cutaneous layer with little subcutaneous fat in the eyelid area, as well as the intricate structure of the eyelids, their mobility and interrelation (Dubois et al., 2016; Jategaonkar et al., 2019).

For repositioning and recontouring of the orbital soft tissues, minimally invasive techniques are advisable, since any open procedure will result in further scar tissue. Both the bone frame and the soft tissue contours and volume must be restored since the bone contours provide the support for the overlying soft tissues and together they contribute to the normal architecture and appearance of the region (Dubois et al., 2016; Siah et al, 2017).

Options for reconstructing the orbital walls and rims include the use of autologous tissues such as bone grafts, composite flaps, or the use of titanium meshes conformed to the three-dimensional shape of the defect. Periorbital soft tissue volume may be augmented using structural fat grafting, that provides additional benefits on improving local scar tissue due to the presence of adipose derived stem cells in the grafted fat (Siah et al, 2017).

Repositioning of the eyelids and periorbital soft tissues is especially important in restoring facial symmetry and minimizing the functional sequelae of lagophthalmos in patients with facial nerve paralysis. In addition to autologous fat trasfer, barbed threads insertion can help the lifting and repositioning of the periorbital soft tissues, as a minimally invasive incisionless procedure. Additional techniques including the insertion of gold weights in the superior eyelid and remodeling of the inferior eyelid for ectropion improvement may be necessary in certain cases but have the disadvantage of further scarring (Guthrie et al., 2019).

Small and medium cutaneous defects in the periorbital region can be managed effectively using skin grafts or various types of local flaps. Local flaps may render more aesthetic results due to the more adequate thickness, as opposed to the thin split thickness skin grafts (Lu et al., 2017). Secondary revisions may be necessary for improving the functional and aesthetic outcomes of the reconstruction since the thickness and texture of the periorbital region are difficult to primarily restore with great fidelity by using adjacent tissues. In addition, postoperative scar tissue may distort the result and may be secondarily improved using autologous fat grafting (Looi et al., 2006; Lu et al., 2017).

More extended defects, involving the contents of the orbital cavity, necessitate more complex reconstructive methods, considering the extent of the tissue loss and the involved anatomical structures. Orbital exenteration sockets can be lined with split thickness skin grafts and the cavity preserved for future episthesis placement (Babu et al., 2016). This approach to reconstruction has the advantage of easy surveillance of tumor recurrence that can be directly observed and diagnosed early. Otherwise, sockets can be filled with a thick muscular flap for complete clothing of the bone walls, especially in regard of the indication for radiotherapy, when good tissue coverage can prevent the onset of complications. On the other hand, a recurrence of the malignancy growing deep to the flap is diagnosed late in the evolution, especially since imaging studies may confuse the initial stages of the recurrence for postoperative or postradiotherapy local changes (Sokoya et al., 2019; Jategaonkar et al., 2019).

The plasty of extended substance loss in the orbital region aims primarily at separating anatomical cavities, in order to ensure isolation of the intracranial space, closure of sino-orbital defects, but also providing skin lining. In this regard, free flaps are often necessary for extended defect closure. Pedicled local or regional flaps, like the temporalis muscle flap or the greater pectoralis musculocutaneous flap, are generally a reliable solution for the plasty of medium sized defects. Depending on the composition of the defect, various types of flaps, including composite flaps, may be indicated (Badhey et al., 2019). Muscle containing free flaps are generally useful in closing cerebrospinal fluid fistulas and isolating the intracranial space, while also providing bulk for filling of the orbital cavity (Jategaonkar et al., 2019).

1.2. INTERDISCIPLINARY TREATMENT IN ORBITAL ENDOCRINOPATHIES

Endocrine orbitopathy, also named Graves' orbitopathy, Graves' ophthalmopathy, thyroid ophthalmopathy, or thyroid eye disease is a chronic autoimmune disorder of the orbit usually associated to thyroid modifications in the context of Graves' disease (Smith, 2010; Wang et al., 2018). Endocrine orbitopathy is usually bilateral but may be asymmetric (Clauser et al., 2012). Its evolution is unpredictable, with progressive, stabilized, and unchanged or spontaneously improving modifications (Kotwal, Stan, 2018). Surgery can improve the quality of life by adapting the orbital volume to its content through orbital expansion and/or decompression and through procedures for functional or aesthetical reasons.

Orbitopathy is a common extrathyroidal feature of Graves' disease. One quarter to half of patients with Graves' disease have or will develop signs of orbitopathy (Braun et al., 2017). The pathogenesis of ophthalmopathy associated with Graves' disease remains poorly understood. Graves' ophthalmopathy, including the orbital manifestations of this autoimmune disorder, results from the accumulation of lymphocytes and deposition of glycosaminoglycans in orbital soft tissues. The initial immune infiltration is followed by irreversible fibrosis and hypertrophy of the extraocular muscles, leading to exophthalmos, diplopia and optic nerve compression. The subsequent enlargement of the orbital fat and of the extraocular muscles displaces the globe in an anterior direction, with consequences regarding the appearance, but also the vision (Li et al., 2018).

The immune infiltration and enlargement of the extraocular muscles, periorbital connective and of the adipose tissue are most commonly found (Clauser et al., 2012). The expansion of the orbital contents inside a cavity with rigid walls, represented by the bony orbit, leads to the compression of the globe, frequently accompanied by an increase in the intraorbital pressure (Stiebel-Kalish et al., 2010; Li et al., 2018). The swelling of the extraocular muscles leads to motility impairment that may aggravate and be accompanied by diplopia as the disease evolves to an active inflammatory stage (Smith, 2010; Clauser et al., 2012). The most frequently involved muscles are the inferior and medial rectus, with a limitation of the upward and lateral gaze, but the superior and lateral rectus may also be involved (Clauser et al., 2012). The initial inflammatory (active) phase usually gets stabilized within one to two years and may even regress (Cozma et al., 2009; Clauser et al., 2012). The chronic inflammation may however be followed by irreversible fibrosis of the extraocular muscles and of other structures of the retroorbital space (Stiebel-Kalish et al., 2010; Clauser et al., 2012). When all the extraocular muscles are enlarged and accompanied by retroorbital congestion and infiltration, they may exert a cone of pressure around the orbital apex, constricting the optic nerve and leading to the acute decrease of visual acuity and even vision loss, phenomenon known as the “orbital apex syndrome” (Blandford et al., 2017). Fibrosis may also involve the levator palpebrae and/or the lower eyelid retractors, causing upper and/or lower eyelid retraction, respectively, with a lack of coordination between eyelid and eye globe movements (Kazim, Gold, 2011). These modifications, together with proptosis, lead to incomplete eyelid closure and chronic corneal exposure to trauma and damage (Sokol et al., 2010).

The orbital signs and symptoms include proptosis, chemosis, congestion of the episcleral and conjunctival blood vessels, elevation of the intraocular pressure, limitation of extraocular motility, and orbital pain (Wickwar et al., 2015; Wang et al., 2018). Compressive optic neuropathy is the most common cause of irreversible visual loss secondary to Graves’ ophthalmopathy. Fortunately, the prevalence of optic neuropathy with visual loss in patients with Graves’ ophthalmopathy is less than five percent (Braun et al., 2017). Proptosis of the globes may lead to a variety of complications that range in severity from cosmetic disfigurement to permanent blindness. To ameliorate the exophthalmos, medical, radiotherapeutic and surgical measures have all been used with varying degrees of success (Genere, Stan, 2019).

Surgical orbital decompression has been used since more than 100 years, when Kroenlein described for the first time a technique of lateral orbit wall removal, allowing the enlargement of the orbital volume. This technique was initially used for the excision of an intraorbital tumor, being subsequently used as a model for the first orbital decompressions performed by Dolinger in 1890 (Dolinger, 1911). The indications of surgical decompression were however limited by its related side effects, sequels and morbidity.

The gradual evolution of surgical and anesthetic techniques decreased the postoperative risks. Therefore, the indications of surgical orbital decompression were extended from patients with major risk of vision loss to other less threatening modifications (McCord, 1985). Surgical decompression further evolved when Olivari added the possibility of intra- and extraconal fat removal (Olivari, 1991).

The symptomatology of Graves' ophthalmopathy is largely influenced by the inefficient venous and lymphatic drainage (Bartalena et al., 2004). An improvement of the orbital drainage is achievable by simultaneous intervention upon the orbital volume, by increasing it through the removal of one or several of its walls, and upon its content, by diminishing it through lipectomy. A combination of these techniques may reduce retrobulbar pressure with at least 8-12 mmHg (Otto et al., 1996).

Another reason for the broadening the indications for orbital decompression is the inconstancy of the results of noninvasive therapeutic strategies. Glucocorticoid administration and external radiation were generally proved to be efficient for the therapy of optic nerve neuropathy and orbital inflammation, but less so for the improvement of proptosis or diplopia, complications that can be efficiently reversed by performing surgical orbital decompression (Strianese, 2017; Wang et al., 2018).

Graves' orbitopathy could be classified into three types: prevalence of fat tissue (Type I), muscle involvement (Type II) and a combination of the two preview types (Type III) (Morax et al., 1997). The type of orbitopathy is very important in choosing the most suited surgical approach - intervention on the bone walls of the orbit versus intervention on the fat tissue. The number of orbital walls or the quantity of fat tissue that need to be removed can be decided depending on both the type and the severity of the orbitopathy (Rootman, 2018). The reduction of proptosis after surgery can be easily predicted. However, the results of surgery regarding diplopia reduction are less predictable (Stell, 2007).

The treatment of Graves' orbitopathy consists in a series of measures in order to maximize the final beneficial result and make it more predictable. For improved and stable results, an accurate control of Graves' disease must be achieved by endocrinologic treatment. Visual disturbances and associated ocular lesions must be promptly diagnosed by ophthalmologic follow-up (Bartalena et al., 2004; Rootman, 2018).

There is no consensus regarding the influence of orbital irradiation before surgery upon the results of orbit decompression. Certain authors suggest that irradiation has no negative effects on the results of surgical therapy for Graves' ophthalmopathy (Baldeschi et al., 2008). Irradiation might however have a negative influence upon the results of decompression if the lipectomy procedure is exclusively used (Richter et al., 2007). When medical treatment and radiotherapy are inefficient, surgical decompression may help to decrease inflammatory signs, but also those of neuropathy and corneal injury, together with the improvement of diplopia, when present (Morax, Badelon, 2009).

A surgical approach of the orbit should be initiated when necessary if the nonsurgical management fails or is followed by incomplete improvement of the orbitopathy. Orbital surgery may improve or even completely reverse all the modifications (Goh, Nab, 2005). Proptosis and motility dysfunction are two main complaints corrected by various surgery techniques. Patients with optic neuropathy, exposure keratopathy or disfiguring proptosis may benefit considerably from decompression methods which allow the enlarged orbital contents to move into the maxillary sinus cavities. Hirsch (Hirsch, Urbanek, 1930) has removed the orbital floor, Walsh (Walsh, Ogura, 1957) has removed the medial wall and the orbital floor by a transantral approach. Mc Cord (McCord, 1981) has obtained the same result via a transconjunctival approach. Depending on the grade of the proptosis it is possible to remove one to four orbital walls (Tallstedt, 1998; Lee et al., 2003). Olivari (Olivari, 1988) has made the first orbital decompression by removing the orbital fat. To limit the surgical risks, Clauser (Clauser, 1991) used a combination of both techniques: the osseous expansion and the fat decompression.

The type of procedure is generally decided in relation to the existing modifications of the orbital tissue, particularly regarding the amount of volume increase of the extraorbital muscles and orbital fat tissue. Different surgical procedures may coexist in the same patient, considering the existing modifications and complaints. Therefore, the techniques used must be adapted individually to the needs of every patient (Cozma et al., 2009; Stiebel-Kalish et al., 2010).

A multidisciplinary team management is necessary in order to achieve the best possible outcomes, including an endocrinologist, an ophthalmologist, a radiologist, and a surgeon, addressing the complex manifestations of the disease, as well as the base-line treatment and follow-up.

From the beginnings of my career, one of my main focuses was improving the functional and aesthetic results for Graves' orbitopathy patients by the interdisciplinary management of this condition. The clinical outcomes have been published in two original articles:

- ✓ **Costan VV**, Costan AR, Bogdanici C, Moisii L, Popescu E, Vulpoi C, Mogos V, Branisteanu D. Surgery for Graves' ophthalmopathy: when and what for? The experience of Iasi. Acta Endo (Buc) 2012; 8(4):575-586.
- ✓ **Costan VV**, Preda C, Bogdanici C, Trandafir D, Costan R, Vicol C, Moisii L, Zbranca E, Voroneanu M. Surgical treatment in Graves ophthalmopathy - case report. Acta Endo (Buc) 2008; 4(3):345-352.

The objective of the study was to determine the outcomes of different techniques of orbital decompression used, in accordance with specific modifications of the orbital contents, related to the bony structure and considering the severity of the complaints, in order to ensure optimal adaptation of the technique to the case particularities and simplify decision making in future surgeries.

1.2.1. Materials and method

We performed a retrospective study by reviewing the medical charts of 41 patients who underwent surgery for Graves' ophthalmopathy between January 2006 and November 2018. Only patients who had a minimum of six months of follow-up were included in the study. The longest follow-up time was 12 years.

The patients were evaluated and followed by a team including endocrinology, ophthalmology, and maxillofacial surgery. An orbital computed tomography (CT) was performed in all patients before surgery, for evaluating the volume and distribution of the orbital fat tissue, as well as the volume of the extraocular muscles. CT was also necessary for excluding a maxillary or ethmoidal sinusitis, or the presence of an orbital tumor.

Information regarding the onset and duration of the disease, the degree of exophthalmos, previous treatments, imaging, surgery indication, the surgical method used, the postoperative outcomes and reinterventions were all documented. The mean proptosis values measured with the Hertel's exophthalmometer preoperatively were compared with the postoperative measurements made 6 months after surgery. The results were statistically analyzed using the Student's T test.

1.2.2. Results

- **Clinical characteristics**

Forty-one patients were included in the study, of which 29 women and 12 men, with a 1:2,4 male to female ratio. All patients presented with proptosis. Proptosis involved measurements greater than 22 mm using the Hertel's exophthalmometer. There were 37 cases presenting with bilateral proptosis and three cases of unilateral exophthalmos. The main addressing complaint was proptosis in 28 cases, and diplopia for the other 12 cases.

A unilateral decreased visual acuity was the main concern in one patient. Additional complaints upon presentation were represented by pain (n=13), retro-ocular tension sensation (n=11), blurred vision (n=10).

- **Therapeutic approach**

In 40 patients, surgery was initiated in the chronic phase of ophthalmopathy, after the normalization of the thyroid function for at least 6 months, and when previous medical orbital decompression failed. Orbital irradiation was performed before surgery in two of the patients. Our study included one case of emergency intervention, performed in a patient with unilateral severe proptosis and decreased visual acuity.

The majority of patients included in our study had bilateral orbital decompressions (38), with a unilateral intervention performed for only 3 patients. Since the surgical technique used and the results can be different in each of the orbits of one patient undergoing bilateral surgery, for a better outlining, the procedures are presented as performed for a number of orbits. Seventy-nine orbits were thus submitted to decompression. A fat decompression alone was performed in 6 orbits. For 73 orbits, the decompression involved both the orbital fat and the bony walls.

The approach used for orbital fat decompression was a superior eyelid blepharoplasty incision for the superior quadrants in all cases. For the inferior quadrants, an inferior transpalpebral approach was performed in 16 cases, while a transconjunctival approach was used in 25 patients. All four quadrants were approached for all the cases of orbital fat decompression. Only the extraconal fat was addressed in 14 cases, while both the extraconal and the intraconal fat compartments were addressed in the other 27 patients undergoing orbital fat decompression. The volume of removed fat tissue, including the intraconal fat, varied between 0.1 and 2.9 mL from the superior compartments and between 0.5 - 2.8 mL from the inferior compartments.

The bony orbital decompression involved the inferior orbital wall in 31 orbits, while for 38 orbits both the inferior and the medial orbital walls were removed. In 18 orbits, the approach to the inferior orbital wall was achieved through the inferior orbital rim and the entire floor of the orbit was removed. In the remaining cases, only the bony wall situated medially to the infraorbital canal was removed.

The upper eyelid position was addressed during orbital fat decompression surgery, by performing a levator aponeurosis recession in 27 cases.

- **Surgical outcomes**

All patients with the entire floor of the orbit removed experienced postoperative hypoesthesia in the territory of the infraorbital nerve, which disappeared in less than two months postoperative in all patients but one, when it persisted for longer than 12 months. There were no complaints of infraorbital nerve hypoesthesia in the patients undergoing removal of the internal part of the orbital floor and medial orbital wall by transconjunctival approach.

From the 12 patients presenting for preoperative diplopia, double vision disappeared after the first two weeks postoperative in 9 patients. The other three cases were directed for further strabismus surgery. In the patients without preoperative diplopia, a transient double vision was present after surgery, but disappeared in between one and two weeks after the orbital decompression. Additional complaints regarding pain, retro-ocular tension feeling, and blurred vision significantly improved in all cases after decompression surgery.

The degree of proptosis measured with the Hertel's exophthalmometer 6 months after surgery, decreased with at least 1 mm in all patients compared to the preoperative measuring. The most important reduction (with 4.2+/-1.7 mm, from 25.4+/-2.7 mm preoperative to 21.3+/-1.6 mm postoperative) was obtained in the 29 patients operated mainly for proptosis reduction ($p < 0.001$).

In the one case of emergency procedure due to unilateral severe ophthalmopathy, the visual acuity in the affected eye improved dramatically after orbital fat decompression with both extraconal and intraconal fat removal. The results regarding the restoration of visual acuity were comparable with the unaffected acuity of the other eye.

In three cases, a blepharoplasty was necessary after decompression surgery due to the remaining excess skin in the superior eyelid. In 7 patients, the superior eyelid retraction still present after decompression surgery was treated by botulinum toxin injections in the levator palpebrae muscle, with good results. Only one patient was diagnosed with an inferior eyelid retraction, 18 months after surgery, and it was corrected with palatal mucosal graft.

A surgical revision was only needed in the one patient with severe orbitopathy on the severely affected side, in order to remove the external orbital wall and more extraconal fat.

The positive postoperative outcomes are demonstrated by three examples of clinical cases, presenting the preoperative appearance and the postoperative results, including the appearance several years after surgery, proving the stability of the results over time, regarding proptosis reduction. (Fig. 1.2.1-1.2.13).

Fig. 1.2.1. Example 1: Graves' ophthalmopathy patient with bilateral proptosis in which a bilateral orbital decompression of the orbital fat and of the orbital floor was performed: preoperative frontal view.

Fig. 1.2.2. Example 1: Preoperative left profile view.

Fig. 1.2.3. Example 1: Postoperative frontal view of the patient 12 years after surgery showing the stable resolution of proptosis

Fig. 1.2.4. Example 1: Left profile view 12 years postoperative.

Fig. 1.2.5. Example 2: Graves' ophthalmopathy patient with bilateral asymmetric proptosis in which a mixed fat and bony decompression of the right orbit and isolated fat decompression of the left orbit were performed: preoperative frontal view

Fig. 1.2.6. Example 2: Preoperative right profile view

Fig. 1.2.7. Example 2: Postoperative frontal view of the patient, 8 years after orbital decompression surgery, showing the restoration of symmetry and resolution of diplopia.

Fig. 1.2.8. Example 2: Postoperative right profile view of the patient, 8 years after orbital decompression surgery.

Fig. 1.2.9. Example 3: Preoperative aspect of a Graves' ophthalmopathy patient in which diplopia was the main concern. A mixed fat and bony decompression surgery were performed: preoperative frontal view during forward gaze, showing the unequal level of the globes.

Fig. 1.2.10. Example 3: Preoperative aspect of the patient during upward gaze showing the movement restriction in the left eye.

Fig. 1.2.11. Example 3: Frontal view of the patient 2 years after bilateral orbital decompression surgery showing the equal level of the globes, as well as the presence of bilateral superior eyelid retraction.

Fig. 1.2.12. Example 3: Frontal view of the patient following the injection of botulinum toxin performed for the superior eyelid retraction, showing normal eyelid position that was stable 10 years after the injection.

Fig. 1.2.13. Example 3: Frontal view of the patient during upward gaze, 12 years after surgery, demonstrating the absence of movement restriction.

1.2.3. Discussions

Surgery for Graves' orbitopathy is indicated mainly in the chronic stage of the disease (Morax, Badelon, 2009), preferably after a minimum of 6 months of orbital inactivity. The need for emergency surgery is quite rare, involving mainly the cases with rapidly decreasing visual acuity due to optic neuropathy (Bartalena et al., 2016; Saeed et al., 2018). In our case series, we followed the same recommendations, establishing the indication for surgery in a multidisciplinary setting, involving an endocrinologist, an ophthalmologist and a maxillofacial surgeon for initiating each stage of the treatment and for follow-up. The majority of the cases included in our study were operated in the quiescent phase of the disease. Our case series included only one emergency procedure for a unilateral decrease in visual acuity. A fat decompression, including the removal of intraconal fat, using the Olivari technique, was effective in restoring visual acuity to normal, even in the absence of bony decompression.

We consider that, besides emergency intervention, there are two other distinct categories of patients with Graves' orbitopathy that greatly benefit from decompression surgery: patients with important proptosis, irrespective of the presence of diplopia, and patients in which diplopia is the most important complaint, but proptosis is non-significant. Other authors (Jernfors et al., 2007; Zosin et al., 2010) consider that orbital inflammation refractory to non-surgical approach may also be an indication for orbital surgery in up to a quarter of patients. The psychological impact for choosing orbital surgery is, however, very important in all situations, since increasing the quality of life or the patients is the desired outcome of both medical and surgical treatment in Graves' orbitopathy (Zosin et al., 2010; Wickwar et al., 2015).

Rundle and Pochin (Rundle, Pochin, 1944) provided a quantitative assessment of proptosis in studies on cadavers, noting that a 1.0 mm increase in proptosis occurred with every 0.67 ml increase in orbital volume, or 6 mm of proptosis can be expected after only a 4 ml increase in orbital contents. Therefore, proptosis reduction necessitates either a reduction of the orbital volume, or a redistribution of the existing amount of tissues. The purpose of decompression surgery is to provide an increased space for the increased orbital content through the partial removal of the bone components of the orbit, as well as reducing the volume by the partial removal of the enlarged orbital fat (Eckstein et al., 2018; Ediriwickrema et al., 2018). Studies have shown that orbital decompression rapidly decreases the intraorbital pressure, while also ensuring an improvement of the venous and lymphatic drainage. As a result, there will be a reduction of the orbital and periorbital edema, as well as a reduction in extraocular muscle volume with a subsequent decrease in proptosis, resolution of double vision and a decreased compression on the optic nerve (Dutton, 2018).

Although, most surgeons follow the treatment guidelines consensually established by the European Group on Graves' Orbitopathy (EUGOGO) (Bartalena et al., 2016), there is an increased variability of the surgical techniques preferred by each for achieving the same results, considering the experience and specialization of the surgeons involved. We achieved best outcomes by performing an associated fat and bony decompression with an accurate preoperative evaluation of the individual anatomic orbital volume changes for establishing the amount of tissue to be removed. We consider that a proper planning is necessary for achieving symmetry of the orbits, while ensuring enough proptosis correction, resolution of diplopia and reducing complications related to orbital surgery.

Like advocated by many authors (Fichter et al., 2012; Strianese, 2017; Dutton, 2018), we used a preoperative orbital CT to evaluate the disposition and quantity of orbital fat, as well as the enlargement of the extraocular muscles. This allowed an accurate planning of the surgical intervention. The presence of large quantities of fat tissue allowed avoiding the removal of more than one orbit wall in many cases of important proptosis.

Dutton (Dutton, 2018) noticed that the most frequently enlarged extraocular muscles- the medial and inferior rectus- are conveniently overlying the thinnest orbital walls- the medial wall and orbital floor. This anatomical fact explains the good results obtained in the reduction of intraocular pressure by removal of the two previously named orbital walls. Such positive outcomes are also outlined in our study, although bony decompression was also associated to fat decompression in all included cases.

Both types of decompression procedures – orbital enlargement through intervention on the bone walls or reduced volume of the orbital contents through lipectomy - have advantages and disadvantages. Some authors (Morax et al, 1997) consider that decompression through intervention on the orbit walls only is more efficient on the reduction of the degree of exophthalmos but has minimal effects on the correction of diplopia. This type of intervention even seems to be followed by an increased postoperative rate of ocurrence or aggravation of diplopia, irrespective of the surgical technique - transantral (Kazim, Gold, 2011) or endoscopical (Schaefer et al., 2003). Regarding an isolated orbital fat decompression procedure, Olivari (Olivari, 1991) states that the removal of a large quantity of fat tissue is accompanied by better functional results, but with the inconvenience of rendering the appearance of “sunken eyes”. Our experience suggests that the coupling of lipectomy and orbital wall removal adapted to the clinical modifications and the radiological features leads to better results, since it allows a more efficient individual adaptation, resulting in a decrease of the inconveniences of each separate technique. We obtained an important reduction in proptosis using this combined technique.

The main drawback of performing orbital surgery is the possibility of new-onset diplopia, even in patients without evidence of preoperative extraocular muscle dysfunction. The postoperative evolution of diplopia is also a question of debate, since the final results vary greatly from surgical teams using the same surgery technique (Korkmaz, Konuk, 2016; Jefferis et al., 2018). For instance, Jernfors (Jernfors et al., 2007) decompressed 78 patients through transantral technique (Walsh, Ogura, 1957) and followed them for 15 years, reporting very good and stable results regarding diplopia. None of the patients complained of postoperatory-onset diplopia and those who had diplopia before surgery, this complication became less disturbing after surgery, or even completely disappeared. We report similar results, even if our experience is limited to a fewer number of patients and the follow-up period is shorter. In our study, there were no cases of initially postoperative occurring persistent double vision. Although the prolapse of the inferior rectus muscle into the maxillary sinus can lead to a restriction of the vertical gaze (Fichter et al., 2012), no such finding was encountered in our study. Myositis and fibrosis are thought to cause the asymmetric enlargement of the extraocular muscles, resulting in restrictive strabismus, most often involving the inferior and the medial rectus muscles (Wang et al., 2018). This is consistent with our findings regarding three cases of existing preoperative diplopia that persisted after surgery due to the asymmetric enlargement of the extraocular muscles that necessitated further strabismus surgery.

An important desiderate in orbital surgery is decreasing the incidence of postoperative infraorbital nerve hypoesthesia. Some authors state that a decrease in the pressure exerted on the infraorbital nerve can be achieved by performing a small osteotomy around the infraorbital opening for rendering the nerve loose (Clauser, Tieghi, 2010). In our experience, this type of approach to the orbital floor, through the temporary removal of the orbital rim, resulted in more cases of postoperative infraorbital nerve hypoesthesia, although transient. Additionally, the transpalpebral approach needed for the inferior orbital rim removal, is associated with more overall complications than the transconjunctival approach.

There are studies that describe a decreased risk of infraorbital nerve damage by the removal of only the internal two thirds of the orbital floor and ethmoidal bone, instead of the entire orbital floor (Morax, Badelon, 2009). This procedure avoids the dissection or contusion of the infraorbital nerve during the removal of the inferior orbital wall, also decreasing the pressure exerted by the orbital contents on the nerve due to the disappearance of bone support. Our experience also showed a decreased rate of postoperative infraorbital nerve hypoesthesia with this technique. An additional advantage is the possibility of using the transconjunctival approach for access to the medial and inferior orbital walls and therefore the absence of visible scars and lower incidence of complications, such as ectropion (Bernardini et al., 2017).

We did not encounter any other complications of decompression surgery like the ones mentioned by other studies, such as sinusitis, mucocele formation, hyposmia, nasolacrimal duct obstruction, entropion (Sellari-Franceschini et al., 2016; Jefferis et al., 2018). The most severe complications reported in the literature for orbital decompression surgery, are represented by cerebrospinal fluid leaks and reduction of visual acuity, associated to trans-nasal classic procedures without an endoscopic control, while transpalpebral and endoscopic techniques are generally associated with a decreased rate of complications (Jefferis et al., 2018).

One of the main reasons for performing an orbital decompression is increasing the patient's comfort and quality of life. Most studies state that orbital discomfort is indeed significantly decreased after surgery, operated subjects describing a lessening of subjective perception of retro-ocular tension (Khan et al., 1995; Wu et al., 2017). This is similar to the results of our study since all patients noticed a reduction of pain and retro-ocular pressure feeling following decompression surgery.

Despite a good result after orbital decompression regarding proptosis reduction and disappearance of diplopia, other tissue changes occur over time in the context of Graves' disease, most often involving the muscular structures, resulting in strabismus or superior eyelid retraction. Thus, in addition to orbital decompression surgery, usually a while after performing this procedure, strabismus surgery, or procedures addressing eyelid retraction may be necessary. There are different theories regarding the etiology of eyelid retraction according to different authors. Multiple mechanisms are involved resulting in a multifactorial etiology in most cases (Dutton, 2018). Many authors advocate the exacerbated action or hypertrophy of the levator palpebrae muscle (Dutton, 2018).

Whenever the intraoperative aspect was suggestive for levator hyperactivity, we performed a levator aponeurosis recession to help the repositioning of the superior eyelid. In seven patients with remaining postoperative superior eyelid retraction, botulinum toxin injection in the levator muscle resulted in positive outcomes. In three of the cases included in our study, the orbital decompression surgery resulted in an excessive length of the upper eyelid, necessitating a blepharoplasty. This is suggestive of a false palpebral retraction due to the draping of the superior eyelid over the proptotic globe, similar to the findings of other authors (Rajabi et al., 2014).

Concluding remarks

In our experience, the association of both bony and fat orbital decompression coupled the advantages of each separate technique, while minimizing the disadvantages. Both the intraconal and the extraconal fat compartments need to be addressed for good functional results, especially in emergency procedures for optic neuropathy. In regard to the bony decompression, the removal of the internal two thirds of the orbital floor and the medial orbital wall, via a transconjunctival approach, resulted in proper reduction of proptosis and the least amount of infraorbital nerve sensory disturbances.

We consider that an accurate multidisciplinary evaluation of each case allows a proper diagnosis, treatment indication and an optimal preoperative planning for achieving good outcomes regarding appearance, symmetry and particularly function, while reducing the complications.

The generally predictable results, the reduced rate of complications and the improvement of the quality of life recommend orbital surgery in the chronic phase of Graves' ophthalmopathy, when exophthalmos or diplopia cause significant discomfort, but also as an emergency procedure, when the risk of vision loss is imminent.

1.3. THE MANAGEMENT OF CAVERNOUS HEMANGIOMAS OF THE ORBIT

Reviewed common vascular lesions in the orbit include capillary (infantile) hemangioma, cavernous hemangioma (solitary venous-lymphatic malformation), and lymphangioma (venous-lymphatic malformation). Benign tumors encountered in the orbit include meningioma, schwannoma, and neurofibroma of the optic nerve sheath. There are also findings of lymphoma, metastasis, rhabdomyosarcoma, and optic glioma malignancies (Syed, 2016; Nair, 2018).

Initially, the general symptomatology of developing orbital tumors is quite poor, as the surrounding tissues adjust to the slowly growing tumor and delay definitive diagnosis. The tumor begins to push out the eyeball only after it reaches about 1 cm and the patient has the vague sensation of tension and bursting in the socket of the eye. As the tumor expands, eyeball protrusion occurs along with eyeball movement limitation and dysopsia. Tumors in the orbital conus cause a relatively rapid increase in the protrusion of eyeballs, deteriorating eyeball mobility and early changes in the eye and fundus (Harris, 2010; Gunduz, Karcioglu, 2015).

Although the term hemangioma is sometimes used to describe certain vascular malformations, it describes a true neoplasm lined by proliferating endothelial cells with vascular channels more appropriately. Capillary hemangiomas are infancy's most common tumors, typically appearing in the first 6 months of life as a reddish macula. A proliferative phase occurs for up to 10 months, followed by a slow phase of involution for up to 10 years. Although typically sporadic, genetic syndromes such as PHACES (Posterior fossa brain malformations, Hemangioma, Arterial lesions, Cardiac abnormalities, and Eye abnormalities) syndrome may occur (Syed, 2016; Bilaniuk, 1999). The preferred method for hemangioma imaging is contrast enhanced MRI (Magnetic Resonance Imaging), although CT can also be considered if the patient cannot be sedated for MRI. The diagnosis is typically well-established clinically, but the measurement of the extent of the lesion and mass effect on adjacent structures is indicated by imaging (Bilaniuk, 1999). The clinical diagnosis can be challenging with deep lesions.

Benign vascular malformations (venous lymphatic malformations) are lymphangiomas that commonly affect children and rarely involve the orbit. They are unencapsulated and consist of fibrous material including blood-filled endothelial lacunae or severe fluid. Lymphangiomas tend to increase suddenly due to intralesional bleeding but may also increase with upper respiratory infection. Symptoms include swelling, intraorbital hemorrhage, ocular proptosis, blepharoptosis, and cellulitis. Ocular complications include astigmatism, corneal exposure, secondary hyperopia, strabism, glaucoma and compressive optic neuropathy (Calandriello et al., 2017).

Lymphangioma has a different appearance and growth pattern despite belonging to the same pathological category as cavernous hemangioma. Lymphangiomas exhibit an infiltrative, trans-spatial growth pattern in keeping with their unencapsulated nature, often involving both intraconal and extraconal compartments and pre-and post-septal compartments, violating fascial planes. CT may show phleboliths in a lesion's venous component and may show bony abnormalities. Compared to brain tissue, venous or solid tumor components are hyperdense on unenhanced CT scans. MRI is accurate to delineate the anatomical location and vascular components, and the levels or menisci filled with fluid can be seen (Perez et al., 2010; Sadick et al., 2017; Nair, 2018).

Cavernous hemangioma is a term widely used to describe a solitary, encapsulated venous-lymphatic malformation, the most common orbital vascular lesion. Typical clinical presentation is mostly painless proptosis (mean 5–6 mm), pain, lid swelling, diplopia, lump, and recurrent vision obstruction. Middle-aged women are the most commonly affected group, and the average duration from onset to onset of symptoms is 4 years (Perezet al., 2010; Syed, 2016). The most common locations are the retrobulbar muscle cone, particularly the lateral aspect of intraconal space. However, a small minority (less than 10 percent) of these lesions are extraconal. Because of stronger texture, cavernous hemangiomas rarely bleed from the surrounding support of rich fibrous tissue. While multifocal and bilateral lesions have been reported, orbital cavernous hemangiomas are typically solitary and unilateral. On early post-contrast images, MRI classically shows nodular enhancement and progressive accumulation of contrast on delayed post-contrast images. For the diagnosis of orbital cavernous hemangioma, 99mTc-RBC scintigraphy (technetium-99m labelled red blood cell scintigraphy) is a reliable and useful procedure. It can be considered as one of the routine clinical screening tools for the diagnosis of orbital cavernous hemangioma and as an ultrasonography and CT complementary investigation (Bilaniuk, 1999; Sadick et al., 2017; Nair, 2018).

The selection of surgical methods for the treatment of primary orbital tumors always depends on the tumor's type of pathological texture, its location within the eye socket (related to the globe and optic nerve) and the direction of its possible penetration.

Orbital pathology is of interest to my practice and therefore I have contributed to the enrichment of the literature regarding cavernous hemangiomas of the orbit, by the content presented in the following article:

- ✓ Costan VV, Sava A, Carauleanu A, Costea CF, Cucu AI, Dimitriu G, Dumitrescu GF, Dumitrescu N, Stoicescu MS, Raftu G, Turliuc MD. Histopathological and clinical characteristics of surgically removed cavernous venous malformations (so-called cavernous hemangiomas) of the orbit. Rev Chim. 2019; 70(1):350-354.

The objective of the study was to retrospectively analyze cases of vascular orbital tumors from our practice, regarding the diagnosis and treatment, in order to evaluate the outcomes and contribute to the existing work regarding this topic.

1.3.1. Materials and method

We reviewed the medical files of patients operated for orbital cavernous hemangiomas over the course of seven years. The procedure was performed in teams involving neurosurgery and maxillofacial surgery. Ophthalmologic consultation was performed before and after surgery, as well as during follow-up. The socio-demographic, clinical, radiological and surgical findings of patients were collected and analyzed retrospectively from the medical records.

We only included cases in which the diagnosis of cavernous hemangioma has been confirmed histologically. All resected specimens have been grossly described and representative samples have been fixed in 10% neutral-buffered formalin and embedded in blocks of paraffin. 4-ìm sections were cut and stained with hematoxylin and eosin (H&E). For this study, two independent pathologists re-examined all slides under routine light microscopy to identify their common histopathological features. Postoperatively, all patients were followed up for at least one year.

1.3.2. Results

- **Clinical and imaging characteristics**

A total of 14 patients with orbital cavernous hemangiomas were treated over seven years. All patients were women and varied between 13 and 57 years of age (mean age was 44.2 years ± 5.7 years). The main presenting sign among the patients in this study was proptosis in ten cases (71.42 %) (Fig. 1.3.1., 1.3.2.), but also diplopia was presented in seven patients (50 %).

The lesion was incidentally discovered in four cases (28.57 %) during imaging evaluations for persistent headache. In 11 cases (78.57 %) the left orbit was affected and the right orbit in 3 cases (21.42 %). No case was involved bilaterally.

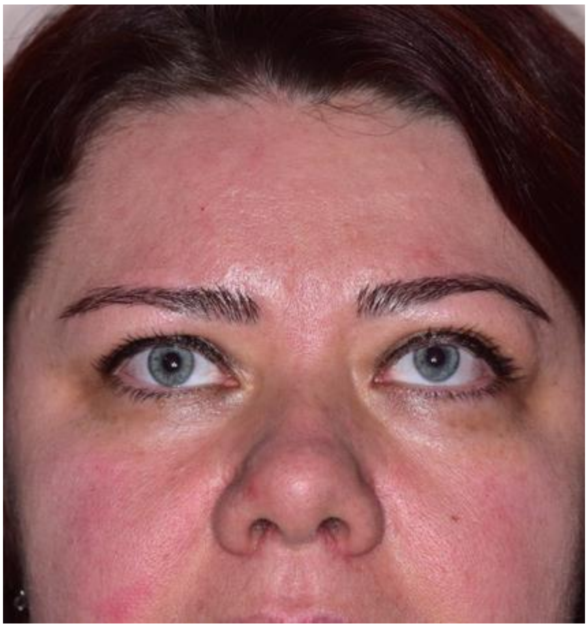

Fig. 1.3.1. Patient with displacement of the left eye opposite to the position of the tumor– open eyes aspect

Fig. 1.3.2. Patient with displacement of the left eye opposite to the position of the tumor– closed eyes aspect

Six patients had MRI preoperatively, five patients had CT and the rest had both investigations without contrast. CT pictures of patients included in the research disclosed a well-defined round smooth tissue tumor. On MRI, the tumor aspect was similar to CT images, but the signal in T1 was isointense compared to the muscle, and hyperintense in T2 compared to the muscle (Fig. 1.3.3.- 1.3.4.).

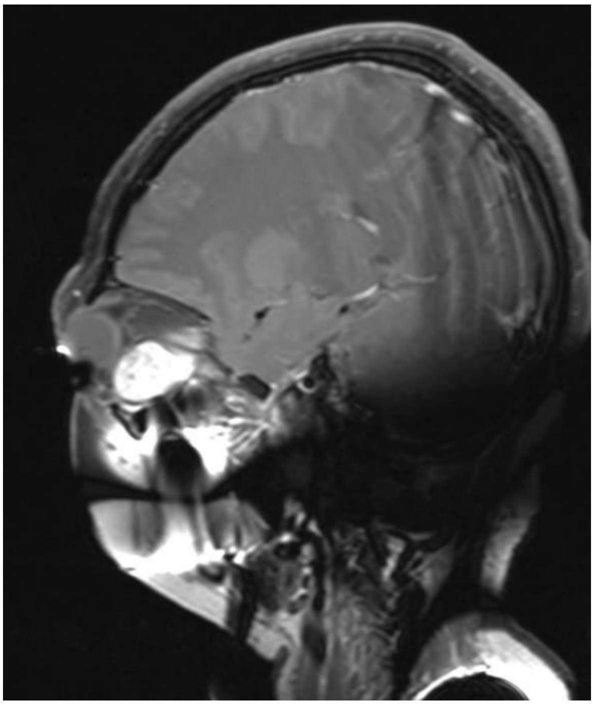

Fig. 1.3.3. MRI aspect in T1 sequence

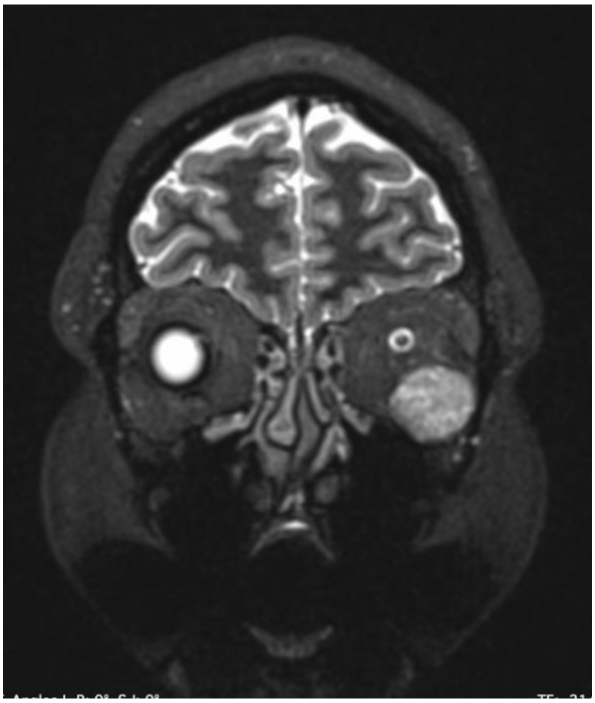

Fig. 1.3.4. MRI aspect in T2 sequence

- **Therapeutic approach and histopathology findings**

The indications for surgical therapy included at least one of the following signs and symptoms: visual impairment, unilateral proptosis progressive and disfiguring, double vision and pain.

In our cases the tumors were in the extraconal inferior or medial orbital compartments, thus an anterior orbitotomy was the elected surgical approach for tumor removal, performed under general anesthesia. Access was achieved using the transconjunctival incision in twelve cases (85.71 %) and the transcutaneous incision in two cases (14.28 %). In all cases, total resection of the tumor was achieved.

The diagnosis of a cavernous hemangioma has been confirmed histologically in all cases. The histopathology exam revealed specific aspects. Grossly, tumors with a reddish gray color and a soft but solid consistency were well circumscribed, for the lesions removed. A sponge-like appearance could be seen on the cut surface.

Microscopically, a fibrous pseudo-capsule encapsulating each of the resected tumors was common in our cases (Fig. 1.3.5.A, 1.3.6.B, 1.3.7.A). Each lesion consisted of large irregular blood-filled vascular channels lined by endothelial cells. These vascular channels were densely knit, but in different quantities separated by fibrous interstitium (Fig. 1.3.5.B, 1.3.6.A, 1.3.7.A). Multilaminar smooth muscle walls with different thicknesses ranging from one to ten layers for the same blood vessel (Fig. 1.3.6.B, 1.3.7.A, 1.3.7.B) had almost all vascular spaces from each lesion analyzed. All cases showed the budding of capillary channels in the interstitium from cavernous spaces (Fig. 1.3.6.C, 1.3.6.D, 1.3.7.A). No intravascular thrombosis or stromal lymphocytes could be seen.

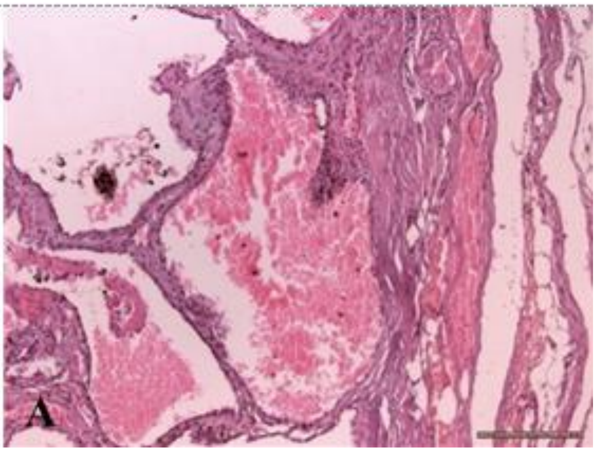

Fig. 1.3.5. A) Histopathological image of an orbital cavernous venous malformation. Large cavernous vascular channels filled with blood and lined by a single layer of flattened endothelial cells and separated by scant connective tissue stroma. A fibrous pseudocapsule surrounded the lesion (H&E staining, x10)

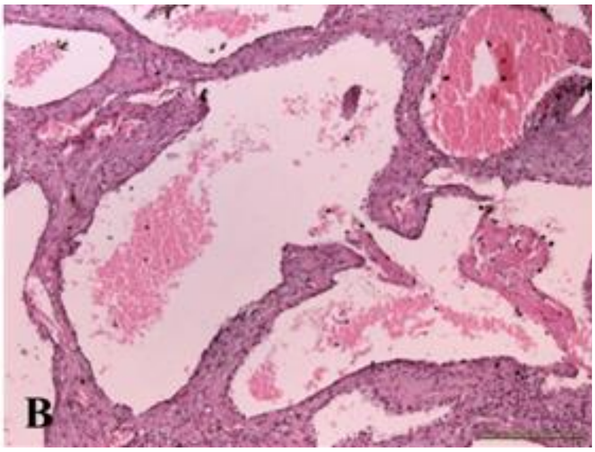

Fig. 1.3.5. B) Histopathological images orbital cavernous venous malformation. The central part of the lesion shows large, endothelium-lined, blood-filled spaces, which are tightly knit and separated by thick septa (H&E staining, x10).

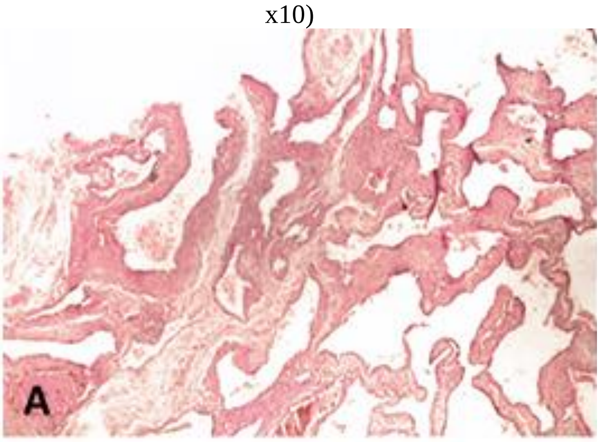

Fig. 1.3.6. A) Histopathological image of another orbital cavernous venous malformation. A). Large, anastomosing vascular spaces, filled with blood and separated by fibrous stroma (H&E staining, x5).

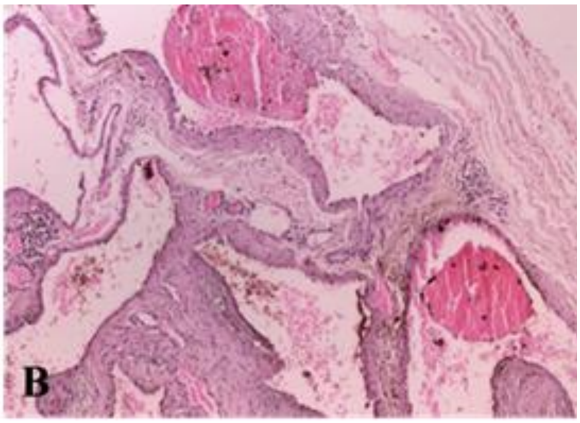

Fig. 1.3.6. B) Well-circumscribed lesion surrounded by a fibrous pseudocapsule and made of large vascular spaces lined by endothelium and multilaminar smooth muscle walls with various thicknesses (H&E staining, x10).

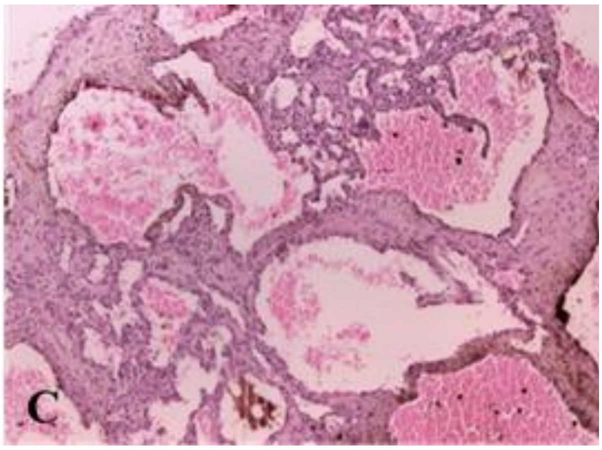

Fig. 1.3.6. C) Microscopical images of budding-off of capillary channels from cavernous spaces into the interstitium (H&E staining, x10).

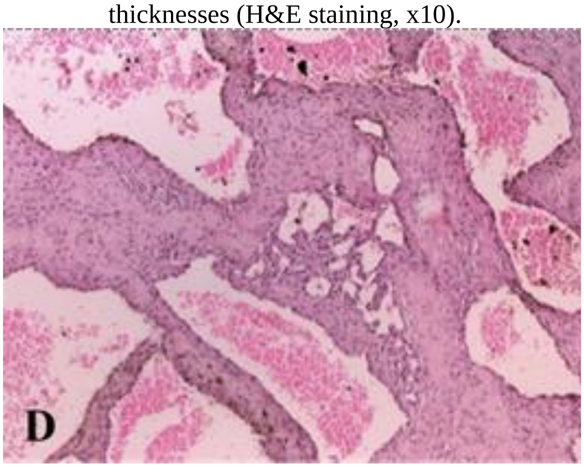

Fig. 1.3.6. D) Microscopical images of budding-off of capillary channels from cavernous spaces into the interstitium (H&E staining, x10).

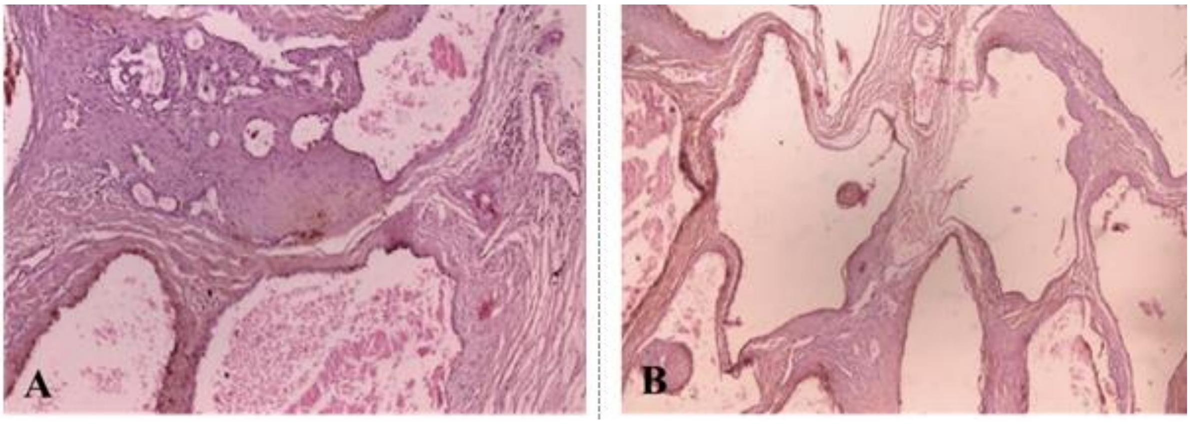

Fig. 1.3.7. Histopathological images of an orbital cavernous venous malformation. A) encapsulated lesion composed of dilated, cavernous vascular spaces lined by a single layer of endothelial cells and separated by connective tissue stroma. Budding-off of capillary channels could be seen (H&E staining, x10). B) Large, anastomosing vascular spaces, filled with blood and separated by fibrous stroma. Vascular spaces showed smooth muscle walls with different thicknesses, ranging from one to 10 layers for the same blood vessel (H&E staining, x5).

- **Surgical outcomes**

The results regarding appearance and function were favorable in all cases. The exophthalmos decreased postoperative and the vision improved (Fig. 1.3.8.- 1.3.9.). Diplopia disappeared after surgery in the patients that initially presented with this complaint. In the four patients diagnosed due to persistent headaches, these symptoms resided after surgery. There were no occurrences of hemorrhagic or infectious postoperative complications and no decrease in vision. No new onset of diplopia was noticed following surgery. The lesions did not recur, as noted at one-year follow-up.

Fig. 1.3.8. The symmetrisation in eye position at one postoperative month – open eyes aspect

Fig. 1.3.9. The symmetrisation in eye position at one postoperative month – closed eyes aspect. Transconjunctival approach has permitted avoidance of visible skin scars

1.3.3. Discussions

Cavernous orbital hemangioma is a benign intraconal space slow-growing lesion. Bilateral cavernous orbital hemangiomas are extremely rare, so in scientific literature only a few cases have been reported. There are extremely rare multiple cavernous hemangiomas of the orbit. There is also a rarity of conjunctival cavernous hemangioma. It often occurs in conjunctival vessels and rarely in scleral, muscular or orbital vessels (Rootman et al., 2014; McNab et al., 2015).

Some reports have introduced a new nomenclature for orbital cavernous hemangioma in recent years because it has been labeled as cavernous venous malformation (Rootman et al., 2014). This entity usually occurs rarely in children but frequently in adult patients between 40 and 60 years of age and is predominantly female (60-70 %) (Ansari, Mafee, 2005; Rootman et al., 2014). Our cases have proven to be all females, with a comparable mean age to other studies (Savoiardo et al., 1983; Harris, 2010; McNab et al., 2015). Recently, a possible explanation has been proposed for sex predilection.

According to Jayaram et al. (2015), the lesions either remained stable or decreased in size in postmenopausal women previously diagnosed with orbital cavernous hemangioma, suggesting that female sex hormones may be involved in the progression of lesions (Jayaram et al., 2015). Cavernous hemangioma is usually solitary and unilateral, involving the left orbit most frequently (McNab et al., 2015). Our study confirms this involvement predominance. In rare cases, this vascular lesion may be associated with other vascular or Maffucci syndrome (consisting of multiple enchondromas and hemangiomas of soft tissue) or blue rubber bleb nevus syndrome (defined by bluish cutaneous and mucosal hemangiomas, enteric hemangiomas and gastrointestinal bleeding) (Johnson et al., 1990; Chang, Rubin, 2002).

The retrobulbar compartment of the orbit is the most common location, particularly the lateral aspect (Ansari, Mafee, 2005; McNab et al., 2015). Exophthalmos, present in 70-95% of cases, is the most common sign and symptom (Scheuerle et al., 2004; Hsu, Hsu, 2011; Calandriello et al., 2017). The average proptosis value is approximately 5 mm at the initial presentation and its progression is estimated to be around 2 mm per year (Bilaniuk, 1999). It can lead to a progressive axial proptosis if the cavernous hemangioma is located intraconally. If it is in the extraconal orbital space, the globe's displacement is opposite to the tumor's position.

Another common symptom is visual acuity impairment (50 %), which occurs when the optic nerve is compressed by the hemangioma. In less than 20 % of cases, local pain, visual field deficiencies, diplopia, and chronic headache may also occur (Scheuerle et al., 2004). Similar to other studies, in almost three quarters of our cases we found exophthalmos, all females, but we found a higher rate of diplopia, probably because of the small sample size. In cases of cavernous hemangiomas, a palpable mass is rarely present and optic atrophy is also occasionally noted.

When the tumor is located near the globe, it can induce hyperopia and choroidal folds that, interestingly, persist even after the hemangioma has been completely removed (Gunduz, Karcioglu, 2015). Symptoms reported less frequently include double vision, swelling of the lid and sensation of the lump. Amaurosis is an unusual symptom associated with multiple intraconal and extraconal orbital lesions, likely due to optic nerve ischemia as this is compressed by retrobulbar mass (Bilaniuk, 1999). Usually, CT and MRI reveal round or ovoid orbital mass well circumscribed. CT shows homogeneous density of soft tissue and can also identify small calcifications or phleboliths (Khan, Sepahdari, 2012; Rosen et al., 2010). MRI shows an isointense T1 signal, a bright T2 signal, dark internal septations and a dark circumferential rim representing a fibrous pseudocapsule (Bilaniuk, 1999; Khan, Sepahdari, 2012; Thorn-Kany et al., 1999). The lesion shows progressive filling on contrast injection and becomes homogeneous. Cavernous hemangioma is considered to be characteristic of this pattern (Gunduz, Karcioglu, 2015).

Differential diagnosis of well-defined orbital lesions includes schwannoma, fibrous histiocytoma, hemangiopericytoma and metastatic lesions, but cavernous hemangioma is the most frequently encountered benign orbital lesion (Gunduz, Karcioglu, 2015). Histopathological examination of a cavernous hemangioma reveals a benign vascular malformation with a well-defined capsule and numerous large dilated vascular channels lined by endothelial cells with fibrous interstitium.

However, some authors conducted immunohistochemical investigations and showed that the vascular channels reacted strongly to the traditional endothelial markers of the blood vessels CD31 (cluster of differentiation 31) and CD34 (cluster of differentiation 34), but were negative to D2-40 (Podoplanin), separating them from lymphangiomas (Gunduz, Karcioglu, 2015). There may be inflammatory cells and macrophages and there may be no or sparse lymphocyte foci. But there are some atypical clinical cases in which inflammatory cells were clearly infiltrated within the lesion interstitium. Blood fills the vascular lumen and regions with intralesional thrombosis that may reflect vascular stasis or slow flow may occur. The stromal structure shows neovascular activity-related perivascular hypercellularity or hyperplastic elements (Ruchman, Flanagan, 1983).

In our cases, a mixture of venous muscle channels and capillary structures has been identified. Thick strands of connective tissue separated all these structures. As reported by other authors (Rosen et al., 2010; Gupta, 2012; Calandriello et al., 2017), we identified variable multilaminar smooth muscle under the endothelium in the walls of large vascular channels, the image being closest to dysplastic veins. We concluded, therefore, that the so-called cavernous orbital hemangioma is a cavernous venous malformation. However, by immunohistochemical staining, Osaki et al. (2013) demonstrated that multilaminar vascular walls stained positively with smooth muscle actine (SMA), but negative with desmin, indicating myofibroblastic differentiation rather than smooth muscle differentiation. Intrinsically, the growth of the lesion can occur through the budding of capillary channels from cavernous spaces into the interstitium (Harris, 2010).

We also identified closely packed capillary vessels in the interstitium in our histological sections. Nagasaka et al. (2007) reported that VEGF (Vascular endothelial growth factor) and Flk-1 (Fetal Liver Kinase 1) immunostaining in their nine specimens were positive in endothelial cells and concluded that both VEGF and its Flk-1 receptor are important for the growth of orbital cavernous hemangioma (Harris, 2010). Proliferative markers are discordantly expressed. In the absence of Mib-1 (Mindbomb homolog 1), PCNA (Proliferating cell nuclear antigen) and Bcl-2 (B-cell lymphoma 2) show positivity and this fact shows its low proliferative potential (Gupta, 2012). As the vascular network progresses towards the adjacent tissue, it induces at the interface a fibrous capsule. The lesion may displace, compress, or incorporate surrounding structures in this expansion process. The relatively mobile muscles, nerves, and vessels can accommodate this slow expansion in the anterior and middle orbit by moving aside and visual impairment only occurs with large lesions. On the other hand, there is no room for displacement in the orbital apex and the vessels and nerves are densely compacted and applied directly (Harris, 2010).

In asymptomatic cases it is recommended that patients be followed with visual field and imaging testing due to the fact that orbital cavernous venous malformation is benign and has a slow growth. Surgery should be considered in symptomatic patients and, although the surgical dissection is fairly easy and bloodless, it should be carefully planned according to the anatomical location of the lesion and its relationship with the anatomo-radiological studies identified in the orbital structures and facial sinuses (Rootman et al., 2014; Gunduz, Karcioglu, 2015). Medicine faces ethical and legal issues in this regard, and surgery should also be planned in accordance with the patient's personal values.

Anterior orbitotomy is commonly used for the excision of extraconal and intraconal lesions, without the orbital apex. (Harris, 2010). The transconjunctival approach can be used successfully for laterally or medially located small tumors to the eyeball (Rosen et al., 2010; Calandriello et al., 2017). In twelve cases, we preferred this approach because it provides excellent orbit exposure, leaves no visible scar and has a lower risk of complications. However, due to the anterior and inferior position of the lesions, we decided to use a subcilliary incision in two cases. In such cases, to release the tumor from the surrounding attachments, it is important to use blunt dissection. In addition, lateral canthotomy may be needed for better exposure in large lesions.

The cryoprobe is an ideal tool for extirpating orbital cavernous venous malformation, with good results reported in reducing intraoperative capsular rupture and bleeding (Scheuerle et al., 2004; Boari et al., 2011; Hsu, Hsu, 2011). A disadvantage of the method is that it is also possible to freeze adjacent structures (Boari et al. 2011). Although such particular methods of achieving a bloodless surgical field are preferred by some surgeons (Scheuerle et al., 2004; Boari et al., 2011), we noted effortless intraorbital dissection, with minimal bleeding that did not require the use of any special methods of hemostasis.

Complications reported in the anterior approach include lid hematoma, mydriasis, vision loss due to direct optic nerve damage, arterial occlusion, or entropion/ectropion (Rootman et al., 2014). No serious or permanent complications were observed in our patients during or after the surgery and good proptosis and diplopia improvement results at follow-up were achieved. There was no recurrence one year after excision because of the benign nature of the lesion and the complete removal.

The endoscopic transnasal approach has recently gained popularity in managing orbital cavernous venous malformation in the medial or inferior orbital compartment (Tsirbas et al., 2005; Bleier et al., 2016). Access to the posterior medial orbit through the ethmoid and sphenoid sinuses can be obtained transnasally. The endonasal endoscopic approach also allows the orbit medial wall to be decompressed. With this approach, however, removing larger lesions is limited. The maxillary sinus transantral approach allows greater access to the posterior orbit floor and facilitates the removal of larger lesions (Harris, 2010). Caldwell-Luc-type procedures were also used to reach orbital lesions in addition to the transnasal endoscopic approach (Calandriello et al., 2017). In our opinion there is no need for such a traumatic approach, the transconjuctival procedure offering a good enough approach to the safe removal of the orbital haemangioma.

Concluding remarks

Our series of cases have shown that orbital cavernous hemangiomas express clinical and imaging characteristics of a benign lesion that usually occur in adult females. Clinical manifestations (exophthalmos, proptosis, diplopia, cephalalgia) constituted the indication for surgery.

We successfully used the anterior orbitotomy approach for tumor removal without significant complications or recurrences. The transconjunctival approach used in most cases allowed good exposure and an adequate access for tumor removal with the advantage of no visible scarring. Excision was easy to perform since the lesions were easy to dissect from the surrounding orbital structures. There was minimal intraoperative bleeding.

The postoperative outcomes were favorable regarding resolution of form, consisting of proptosis reduction, but also function, in regard of disappearance of double vision and headaches. Thus, the quality of life of the patients improved following surgery. The good results were stable in time at one-year follow-up.

1.4. THE MANAGEMENT OF TUMORS EXTENDED TO THE ORBIT FROM THE SURROUNDING STRUCTURES

1.4.1. The management of sinus tumors extended to the orbit

Maxillary sinus tumors are relatively rare since less than 2% of the malignant tumors of the upper respiratory and digestive tract involve the maxillary sinus (Heatly, 1953; Amirith, 2016). One characteristic is that these tumors are often discovered at a later stage due to the fact that the symptoms mimic those caused by inflammatory diseases which includes: nasal obstruction (35%), epistaxis (25%), pain (59%), facial edema (38%), oral symptoms (40%) (Jham et al., 2006), sinus pressure can also be a clinical symptom (Carrau et al., 1999). Moreover, the patient can be completely asymptomatic. Quite frequent, standard radiographic images can be misleading with cases of sinusal tumors misdiagnosed as chronic sinusitis.

Due to the anatomy of the region with close relation between the maxillary sinus and the orbit, these two anatomic entities being separated by only the orbital floor. This can be further weakened by the passage of the infraorbital floor, and to the fact that sinus tumors are often discovered at a later stage, orbital involvement being usually present (Amirith, 2016). This fact determines eye related symptoms such as off axis proptosis, diplopia, epiphora eye movement impairment or even loss of visual acuity determined by orbital nerve compression.

I constantly attempted to improve the treatment methods for sinus tumors with orbital extension. The results achieved are outlined in the following article on this subject:

- ✓ Costan VV, Popescu E, Stratulat SI. A New approach to aesthetic maxillofacial surgery: surgical treatment of unilateral exophthalmos due to maxillary sinus muccocele. J Craniofac Surg. 2013; 24(3):914-916.

The objective of the study was to assess the results obtained in the treatment of different tumors involving the paranasal sinuses and orbit, in order to improve the future management of such cases, refine surgical techniques and improve surgical outcomes.

1.4.1.1. Materials and methods

The records of patients diagnosed with sinus tumors invading the orbit, over the last 10 years were reviewed. Both benign and malignant tumors were included. Surgery was performed in mixed teams involving maxillofacial surgery, neurosurgery, ophthalmology, depending on the degree of tumor extension. The information regarding diagnosis, type of surgery, reconstruction, postoperative outcome was documented. Patients were followed for at least one year after tumor removal, with a maximum follow-up time of nine years.

1.4.1.2. Results

- **Clinical characteristics**

A total of 35 patients (11 women and 24 men) with ages between 8 and 79 years old were identified and included. Nine patients presented benign tumors (3 cases of ossifying fibroma, 4 cases of mucocele and 2 cases of fibrous dysplasia). The other 26 were diagnosed with malignant tumors originating from the maxillary sinus (9 cases of squamous cell carcinoma, 5 cases of adenoid cystic carcinoma, 5 cases of undifferentiated carcinoma, 4 cases of mucoepidermoid carcinoma, 2 cases of metastasis from renal carcinoma, and one case of achromic melanoma).

- **Therapeutic approach**

From the overall included cases, 27 patients underwent surgical treatment for tumor removal. For the other 8 patients, ablation surgery was not indicated due to the extension of the tumor (5 cases), or due to the presence of comorbidities (2 cases). One patient refused the surgical treatment.

For the benign tumors detailed below, the access was performed using a transfacial approach with a Le fort I osteotomy (3 patients), an inferior eyelid incision (1 case), a transantral approach (1 case), endoscopic endonasal approach (3 cases), a Liston-Nelaton approach (1 case).

For three patients with extended ossifying fibroma, the access for the tumor resection was gained by trans-facial approach associated with Le Fort I osteotomy. After tumor resection, the maxillary bones were realigned, and fixation was performed using titanium plates. No complications were noted with this approach.

For one case of fibrous dysplasia (Fig. 1.4.1.1.- 1.4.1.7.), the access for tumor resection was achieved through an inferior eyelid incision. In this case, following tumor removal, it was taking the decision to use a titanium mesh was used to reconstruct the inferior orbital wall. This attitude was necessary for rendering support and ensuring the correct position of the eye globe. In another case of fibrous dysplasia, the access was acquired through transantral fashion.

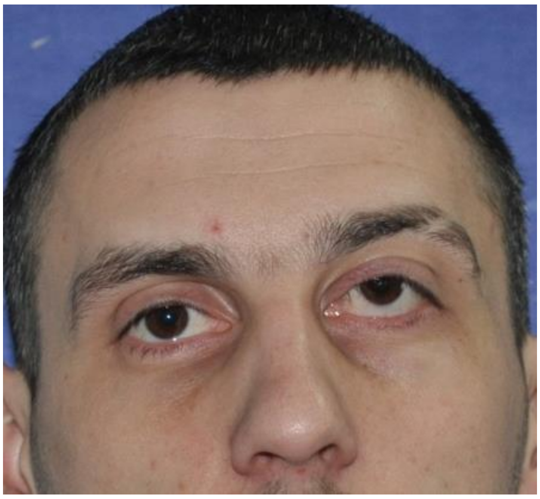

Fig. 1.4.1.1. Example 1: Patient with fibrous dysplasia and displacement of the left eye opposite to the position of the tumor- open eyes aspect

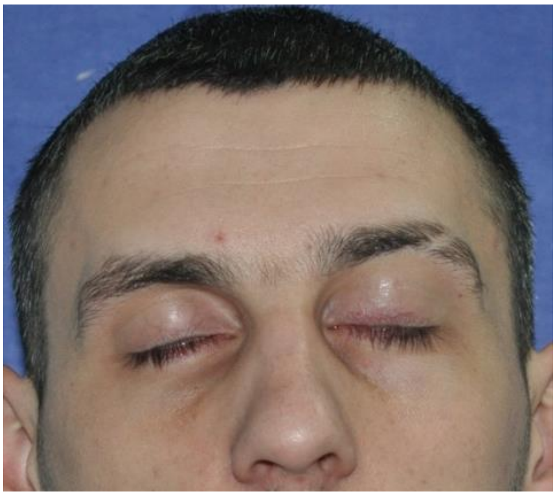

Fig. 1.4.1.2. Example 1: Patient with fibrous dysplasia and displacement of the left eye opposite to the position of the tumor- closed eyes aspect

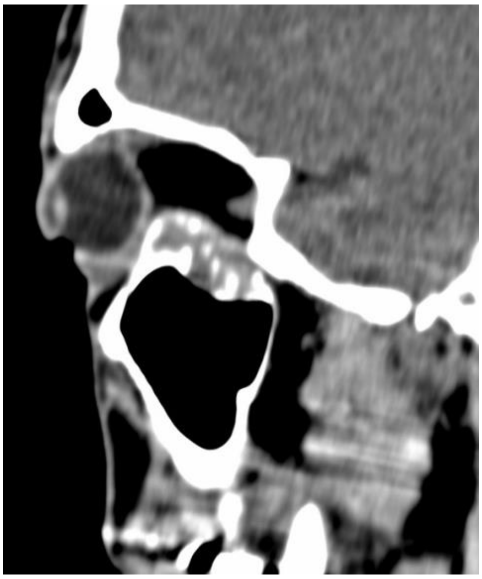

Fig. 1.4.1.3. Example 1: Patient with fibrous dysplasia and displacement of the left eye due to a fibrous dysplasia at the floor of the orbit – CT sagittal aspect

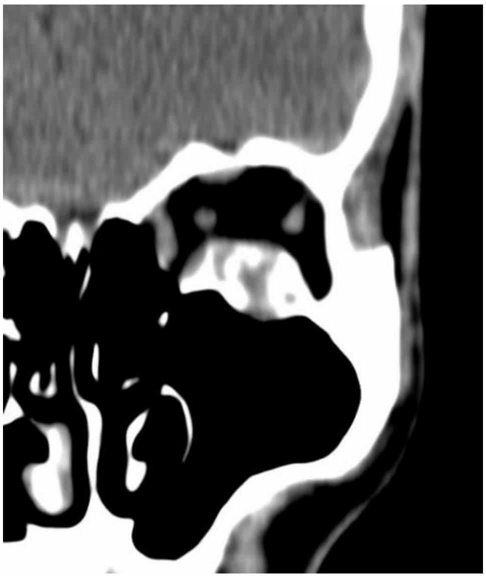

Fig. 1.4.1.4. Example 1: Patient with displacement of the left eye due to a fibrous dysplasia at the floor of the orbit – CT coronal view

Fig. 1.4.1.5. Example 1: Intraoperative aspect after tumor removal

Fig. 1.4.1.6. Example 1: Intraoperative aspect after defect reconstruction using a titanium mesh

Fig. 1.4.1.7. Example 1: Six years postoperative aspect with maintaining of a normal position of the eye

For three cases of paranasal sinus mucocele with orbital extension, the most suitable access was considered the endonasal access with endoscopic control. This attitude was considered due to the important development of the cysts into the nasal cavity, with local bone erosion. Through this way was performed the opening of the cysts into the nasal cavity. This was effective in stopping the development of the mucocele, as well preserving the anatomical structures of the midface in a normal relation.

The fourth case of maxillary sinus mucocele invading the orbit, presented with right proptosis resulting in unilateral diplopia as single symptom. The cyst eroded the inferior orbital wall and anterior sinus wall, extending through malar bone into the subcutaneous region of the malar area. The surgical treatment consisted in removal of the mucocele with the preservation of the infraorbital nerve. The resulting bone defect was reconstructed using an osteo-fascial temporoparietal flap with 2 bone fragments form the parietal bone (Fig. 1.4.1.8. – 1.4.1.13.). Using this kind of flap, at the same time was reconstructed both floor of the orbit and the malar bone eminence. Autologous fat grafting was used as secondary plasty for rendering facial symmetry in the zygomatic and genian regions and restoring soft tissue volumes.

Fig. 1.4.1.8. Example 2: Clinical aspect of a patient with a maxillary sinus mucocele with orbital extension associated with protrusion and diplopia

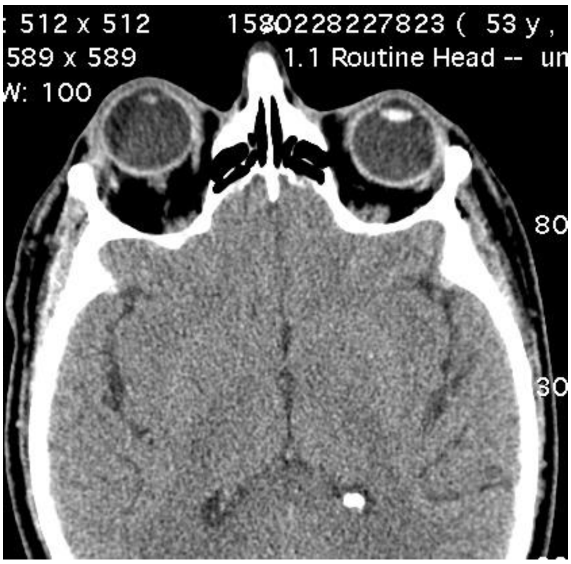

Fig. 1.4.1.9. Example 2: CT axial view showing the presence of the right proptosis

Fig. 1.4.1.10. Example 2: CT Coronal view showing the presence of the right maxillary sinus mucocele extended in orbit

Fig. 1.4.1.11. Example 2: Intraoperative aspect of the osseous defect, with preservation of the infraorbital nerve

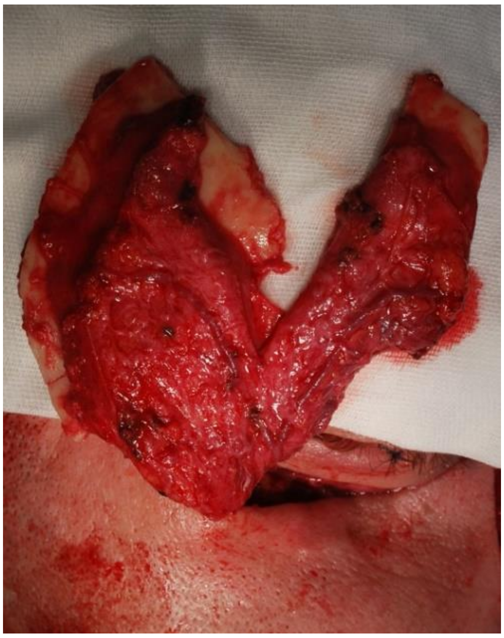

Fig. 1.4.1.12. Example 2: Intraoperative aspect with the osteofascial temporoparietal flap used for the reconstruction of the periorbital osseous defect

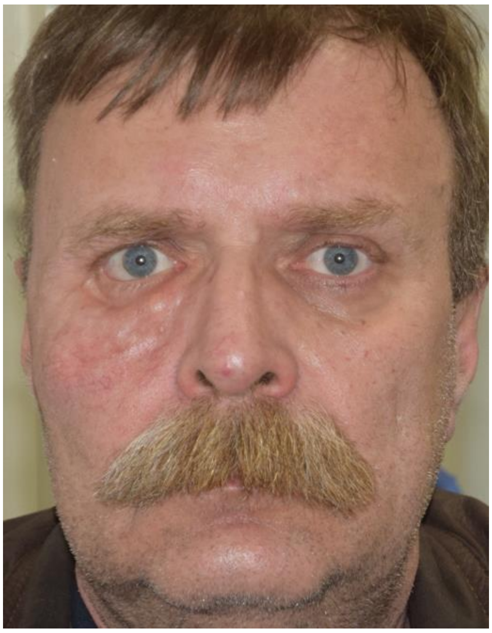

Fig. 1.4.1.13. Example 2: Clinical aspect 9 years after cystectomy and reconstruction of the bone and soft tissue defect

In the cases diagnosed with sinus malignancies extended to the orbit, the surgical treatment consisted of tumoral excision through maxillectomy associated with orbital exenteration in 7 cases. In the other 11 patients that underwent removal surgery, the ablation included a maxillectomy, but an orbital exenteration was not necessary, since only the inferior or medial bony orbital walls were invaded, without trespassing of the orbital periosteum. The approach used in all cases of maxillectomy was a Weber-Ferguson type of incision. In cases where the alveolar bone was also invaded and an infrastructure resection was needed, the function was restored by use of an obturator prosthesis. The orbital exenteration sockets were covered by temporalis muscle flap in four cases, while in the other three patients, the defect was left for secondary healing. In cases where the alveolar bone was not involved by tumor and nor was the orbital content or the skin lining, a reconstruction was not therefore needed (Fig. 1.4.1.14.- 1.4.1.17.).

Fig. 1.4.1.14. Example 3: Patient with displacement of the right eye due to renal neoplasia metastasis into the maxillary bone, extended into the right orbit and ethmoid bones

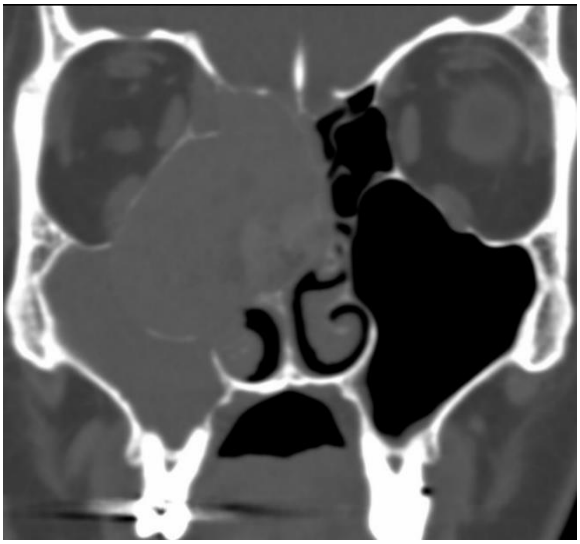

Fig. 1.4.1.15. Example 3: Patient with displacement of the right eye due to an osteolytic tumor involving ethmoid bones, maxillary sinus and orbit – CT coronal aspect

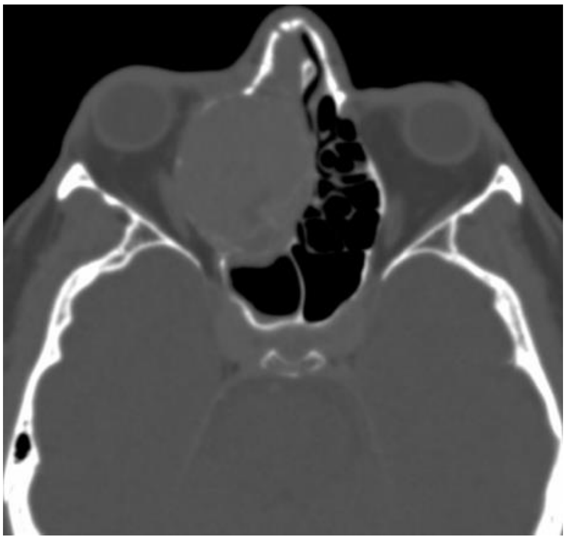

Fig. 1.4.1.16. Example 3: Patient with displacement of the right eye due to an osteolytic tumor involving ethmoid bones and orbit – CT axial aspect

Fig. 1.4.1.17. Example 3: One-year postoperative aspect after tumor removal through a transfacial approach with preservation of alveolar bone.

- **Surgical outcomes**

For eight cases of benign tumors extended to the orbit, the initial postoperative outcome was favorable regarding aesthetics and function. In one case, of the extended mucocele previously described, although good function was achieved primarily, further autologous fat injection was necessary to restore facial symmetry, but with positive final outcomes regarding facial appearance. The positive outcomes were maintained over time at one-year follow-up and further.

In the malignant tumor group, regardless of the type of reconstruction performed, there were good results regarding the complete tumor removal, with absence of recurrence at one-year follow-up and further. Acceptable function was achieved in regard of masticatory, deglutition and phonation in patients with obturator prosthesis reconstructions. In cases of orbital exenteration, the orbital sockets healed well, with a longer healing time in the ones undergoing secondary healing.

1.4.1.3. Discussions

The initial symptomatology associated with the presence of sinus tumors, such as nasal congestion, nasal discharge, pressure, the sensation of midface fullness and epiphora due to the obstruction of the naso-lacrimal duct, mimic those of inflammatory sinus disorders. Furthermore, the obstruction determined by the tumor, often causes superimposed inflammatory episodes that lead to the underestimation of the condition and an incomplete diagnosis. In addition, the images on the conventional x-rays (sinus opacification) are also remarkably similar to the aspect encountered in common inflammatory sinus conditions (Lenworth et al., 1984). Therefore, the true diagnosis is usually overlooked initially and often the tumoral lesion is diagnosed in more advanced stages. All of this and the anatomy of the region can lead to the involvement of the orbit with more than 50 % of patients with sinus tumors accusing symptoms related to eyes and orbit (Myes, Oxford, 2004) such as off axis proptosis, diplopia, eye movement impairment and loss of vision.

For an early diagnosis and for accurately establishing the extent of local invasion, CT scans with slices centered on the floor of the sinus and orbit and/or MRI showing the involvement of soft tissues are becoming indispensable for the evaluation and treatment planning of sinus tumors (Suarez et al., 2008).

The maxillary sinus mucocele is among the common benign tumors that can affect the orbit. Most often the ophthalmic symptomatology is the most prominent manifestation of the tumor (Salam et al., 2012) representing 7% of all orbital tumors and 2.7% of nonendocrine related exophthalmos (Palmer-Hall et al., 1997). The mucoceles are cystic lesions with mucoid content and can appear as a result of the obstruction of the ostium that appears usually after sinus surgery due to sequestration of sinus mucosa (Kaltreider, Dortzbach, 1988) or postoperative fibrous septation of the antrum (Som, Shugar, 1980). The patient may present facial deformity, unilateral exophthalmia which leads to diplopia. Sometimes, eye related symptoms are the only presenting sign, as found in one of the benign tumor patients included in our study.

The treatment for the maxillary sinus mucocele is usually endoscopic with the drainage of the cystic lesion and the enlargement of the sinus ostium although recurrences after these procedures are cited. Sometimes the lesion erodes the surrounding bone, thus leading to the need for reconstructive surgery for restoring the face aesthetics and the shape of the orbit as precisely as possible. For achieving this, a number of solutions are available such as titanium mesh, bone grafts, pedicled locoregional or free transferred flaps, or an association of several methods. In one of our extended mucocele cases, the extensive defect caused by the extension of the cyst with bone erosion, determined us to perform defect reconstruction, by using a fasciocutaneous temporoparietal flap with 2 bone fragments form the parietal bone. We additionally used autologous fat grafting as secondary plasty, to refine the facial symmetry results.

Fibro-osseous lesions that can affect the maxillary sinus and the orbit comprise of osteomas, ossifying fibromas and fibrous dysplasia. Whereas some are diagnosed histologically, all of them require a combined evaluation of clinical, microscopic and radiologic features (Arroyo et al., 1991; El-Mofty, 2014). Fibrous dysplasia is characterized by the replacement of normal bone with fibrous tissue and immature bone, inadequately mineralized. It can affect a single bone or multiple. Monostotic fibrous dysplasia affects the craniofacial skeleton in 25% of the cases (El-Mofty, 2014). Fibrous dysplasia affects growing bones. Thus, it is usually diagnosed in childhood and stabilizes in adulthood (Arroyo et al., 1991; El-Mofty, 2014).

Radiologically, fibrous dysplasia lesions appear as mixed radiopaque and radiolucent images giving the characteristic "ground glass" appearance. For the craniofacial skeleton, fibrous dysplasia mostly affects the maxillary-zygomatic complex (Arroyo et al., 1991; El-Mofty, 2014). In some cases, this pathology can lead to visual impairment due to compression of the optic canals thus the need for surgical orbital decompression (Arroyo et al., 1991). In other cases, like one of the patients from our study group, the fibrous dysplasia causes displacement of the eye with aesthetic and functional consequences. We accurately restored the orbital floor after tumor resection and successfully restored the position of the globe, as well as function for our patient. We considered titanium mesh to be a valuable reconstructive material due to its properties of biocompatibility and malleability, while also providing strength.

Ossifying fibromas are bone producing fibrous lesions that are separated into two main entities: ossifying fibroma of odontogenic origin and juvenile ossifying fibroma. Radiologically are described as sharp unilocular, monostotic well-defined radiolucent lesion with various degrees of opacification (Arroyo et al., 1991; El-Mofty, 2014; Borumandi et al., 2013). In our experience, the complete removal of the lesions was possible despite the orbital extension of the lesion, by using a transfacial approach and Le Fort I osteotomy. Tumor removal was followed by the accurate repositioning of the maxilla using osteosynthesis material and thus no significant esthetic of functional disturbances were noted after surgery.

The treatment for benign maxillary sinus tumors invading the orbit should consider all aspects, including the full removal of the lesion, the functional result, and the aesthetic outcome (McCary et al., 1994; Wormald et al., 2003; Castelnuovo et al., 2009). In our case series of benign sinus tumors with orbital extension, we had good outcomes on all aspects. We consider this to be due to performing the reconstruction of the supporting bony structures where indicated, at the same session with tumor removal. Indication for reconstruction is necessary, since the expectations of patients are high regarding both function and aesthetics, in cases of benign tumor surgery.

Maxillary sinus malignant tumors frequently involve the orbit, with 50% of the patients accusing visual symptoms such as epiphora, proptosis and diplopia (Lundi, 1983). This involvement can be used as a prognostic predictor as stated by Suarez et al. In a study of 57 patients who underwent maxillectomy, involvement of the orbit was associated with a 5-year survival rate of 17% as opposed to 49% when the orbit was not involved (Nazar et al., 2004). Another important prognostic predictor used is the tumor histology, malignant melanoma having the worst prognosis while chondrosarcoma having the best. The most common histologic types, adenocarcinoma and squamous cell carcinoma have a medium prognosis with regards to the survival rate (Iannetti et al., 2005; Ganly et al., 2005).

Since the early stage diagnostic of maxillary sinus tumors is difficult, the symptoms mimicking those of an inflammatory sinus disease and accentuated by the fact that malignant tumors can be confused on standard radiographic images as chronic sinusitis, these are diagnosed at a later stage. This makes the invasion of the orbit even more probable, the ophthalmic signs being sometimes the first symptoms the patient describes. Furthermore, the orbital floor bone is thin further weakened by the passage of the infraorbital nerve. Once the periosteum of the orbit has been invaded there are no barriers against tumoral expansion. With regards to preservation of the contents of the orbit, there is no universal consensus for orbit evisceration (Matsumoto, Yahagihara, 1892; Iannetti et al., 2005). We considered that invasion beyond the orbital periosteum into the orbital fat is an indication of exenteration and obtained accurate tumor ablation by this method of decision.

The treatment for the maxillary sinus malignant tumors consists of surgical removal of the tumor extended to the maxillary bone and orbital exenteration if required (Nazar et al., 2004; Iannetti et al., 2005). Depending on the case, facial degloving or median/paramedian incisions can be used for access. We achieved good access using the Weber-Ferguson approach for performing maxillectomy.

Following tumor removal, a large cavity results, which communicates with the nose, mouth and pharynx. This cavity generally needs to be filled. In case of tumors limited to the maxillary sinus, removed by maxillectomy, an obturator prosthesis is usually sufficient for providing bulk. For larger cavities muscle flaps from the temporalis muscle can be used (Matsumoto, Yahagihara, 1892; Iannetti et al., 2005). We used the same plasty methods in our case series. We consider that the obturator is suitable for most defects not involving the skin, since it provides quick function resumption after maxillectomy by separating cavities, possibility to restore the lost dentition, as well as filling spaces. A good contour of the soft tissues is also rendered during the wear of the obturator. The temporalis flap is, in our experience, a reliable flap for orbital socket coverage. Secondary healing takes longer time but is also effective when indication is adequate. With proper tumor ablation and reconstruction, even patients with extended tumor involving the orbit can have a good life quality with few postoperative complications.

Concluding remarks

Surgery for tumors of the paranasal sinuses extending to the orbit involves the use of extended approaches for optimal access allowing complete tumor removal. The removal of benign tumors with orbital extension raises concerns related to the preservation of orbital structures and avoiding unnecessary injury, as well as postoperative complications. Additionally, reconstructive procedures should be aimed at reconstructing the walls of the orbit for rendering support to the orbital content and minimize functional deficits. We achieved good result in this aspect by using composite flaps, or titanium mesh for the reconstruction of the orbital frame.

With reference to malignant tumor removal, the main concerns are regarding the indication for orbital exenteration, considering the psycho-social consequences of such extensive surgery. The plasty of extended defects requires the mastery of a wide range of reconstructive techniques for ensuring optimal outcomes with minimal complications.

1.4.2. The management of malignant tumors of the ocular adnexa extended to the orbit

Periorbital non-melanoma cutaneous malignancies are common encounters, making up for approximately 5 to 10 % of all skin cancers (Gerring et al., 2017). Basal cell carcinoma is the main type of malignancy involving the periorbital skin, representing approximately 90% of lesions. It is more commonly found on the inferior eyelid and medial canthal area, while sebaceous gland carcinoma is encountered mainly in the superior eyelid region. Squamous cell carcinoma and sebaceous gland carcinomas each account for less than 10% of periocular skin malignancies. Orbital invasion is reported in less than 4% of cases and it is a more likely occurrence in older patients with neglected large lesions located in the medial canthal area, in patients with a history of previously excised skin malignancies and the presence of local recurrence, as well as in association with aggressive histologic subtypes and the ones expressing perineural invasion (Iuliano et al., 2012; Furdova, Lukacko, 2017).

Another common sites for the development of malignant tumors are the ocular adnexa, particularly the eyelids and the conjunctiva. In the initial stages, they are often overlooked by the patient due to the absence of pain and functional impairment. Therefore, the tumor development leads invariably towards orbital invasion, due to the proximity of all the orbital structures and the absence of anatomical barriers to the tumor spread once the malignancy has reached the orbital fat. The treatment is thus complicated and most often implies an exenteration for tumor control, as well as an adequate reconstruction method (Gerring et al., 2017; Furdova, Lukacko, 2017).

The infiltration of intra-orbital structures can be clinically silent in one third of cases (Gerring et al., 2017). If not accurately diagnosed, it can lead to residual tumor and the onset of local recurrence, with a worse overall prognosis. Clinically apparent orbital invasion is generally associated with large aggressive tumors and the surgical treatment can therefore lead to significant morbidity and deformity. The indications for orbital exenteration must be carefully considered for ensuring oncologic safety with minimal morbidity. The accurate diagnosis of the extent of tissue invasion and proper surgical planning can help decide the best option (Gichuhi, Sagoo, 2016).

Conjunctival invasive squamous cell carcinoma (CISCC) is a malignant tumor of the conjunctiva, with varying degrees of differentiation and invading the depth of the conjunctiva, surpassing the basal membrane (Stagg et al., 2014). The incidence of CISCC is 0.1 per 100 000 people per year, with Africa having the highest incidence of 1.3 per 100 000 people per year (Gichuhi, Sagoo, 2016). This neoplasia affects twice as many men than women (Malik, Sheikh 1979; Grossniklaus et al., 1987; Katz et al., 1988). Epidemiological studies incriminate UV (ultraviolet) radiation (290–320 nm) as the most important pathophysiologic agent (Newton et. al. 1996, Lee et. al. 1994) as it induces point mutation in the p53 tumor suppressor protein. CISCC occurs in immunocompromised patients or those affected by albinism or xeroderma pigmentosum (Grossniklaus et al., 1987). It develops at the level of the limbus on a preexisting carcinoma in situ, solar keratosis or epithelial dysplasia (Zimmerman, 1964; Grossniklaus et al., 1987; Katz et al., 1988). Patients with CISCC present the ophthalmologist because of a conjunctival foreign body sensation, conjunctival congestion, and the appearance of a tumor on the surface of the eyeball (Stagg et al., 2014). The tumor mass is initially mobile on the conjunctiva, but in the advanced stages it adheres to the eyeball showing scleral infiltration. Sometimes clinical exam cannot reveal the true size of the lesion, this appearing smaller than it really is, especially when it invades the eyeball structures and the tissues of the orbit (Gichuhi, Sagoo, 2016).

Regarding our experience in the surgical treatment of ocular adnexa tumors extended to the orbit, we published the following article:

- ✓ Todireasa AI, Costan VV*, Popescu MR, Ciocoiu M. Conjunctival invasive poorly differentiated squamous cell carcinoma in a 91-year-old female patient. Rom J Morphol Embryol 2018; 59(1):375-380.

The purpose of this study was to present our experience regarding the surgical management of skin and conjunctival tumors with orbital extension, focusing on the main challenges encountered regarding the extent of tissue removal, the options for reconstruction and the associated complications.

1.4.2.1. Materials and method

We performed a review of patients diagnosed with periocular skin and conjunctival malignancies in between January 2013 and April 2018. We included only the patients who had clinical or imaging evidence of orbital invasion and were diagnosed with non-melanoma skin cancer and conjunctival invasive squamous cell carcinoma. Patients with unresectable tumors were excluded from the study, as well as patients who did not undergo tumor removal due to contraindication or due to the patient’s refusal. Patients diagnosed with skin invasion from malignancies arising in the adjacent orbital or sino-nasal structures, according to the history of the disease and the final histology, were also excluded from the study. The medical charts of all the patients included in the study were analyzed for information regarding the clinical signs, the tumor location and size, the diagnosis of orbital invasion, the type of tumor removal procedure and reconstruction, the postoperative complications and outcomes. The procedures were performed in mixed teams including maxillofacial surgery, ophthalmology, and neurosurgery, depending on the extent of invasion. Patients included in the study were followed for at least one year after surgery.

1.4.2.2. Results

- **Clinical characteristics**

A total of 21 patients with squamous cell carcinoma and basal cell carcinoma skin cancer, as well as conjunctival squamous cell carcinomas extended to the orbit were identified. There were 12 men and 9 women, aged between 57 and 83 years old. Three patients had recurrent tumors from previously operated carcinomas in the same region. Four of them had performed preoperative radiotherapy. Three patients had a history of skin cancer surgery in other head and neck regions, and two patients had previous surgery for cutaneous malignancies in other regions of the body. There were 14 cases of squamous cell carcinomas, six basal cell carcinomas and one glandular carcinoma.

The initial location of the tumor was at the level of the inferior eyelid in eight cases, the superior eyelid in five patients, the medial canthus in two, lateral canthus in one patient, the nasal region in one case, conjunctiva in three patients, the genian region in one patient. Upon presentation, 18 patients had associated clinical signs suggestive for orbital invasion, consisting of exophthalmos (8), globe displacement (7), limited eye movements (5), diplopia (8), infraorbital hypoesthesia (2), visual impairment (8) and tumor adherent to the subjacent bone on palpation (9). In the other three cases, the patients had no obvious clinical signs of orbital invasion.

Paraclinical investigations, CT in 9 cases and MRI in 12 patients, were necessary for determining the tumor spread and diagnosing orbital invasion. Associated clinical findings and symptoms were the presence of a palpable mass in 21 cases, pain in nine patients, bleeding in 14, epiphora in six cases. The greatest external tumor diameter was 6 cm, while the smallest tumor was 3 cm.

- **Therapeutic management**

Tumor removal was performed in all patients after histological confirmation by incisional biopsy. Orbital exenteration was performed in 15 cases and an extended orbital exenteration to the surrounding structures was necessary in six patients. Partial preservation of one or both eyelids was performed in eighteen cases.

The exenteration defect was covered by a split thickness skin graft in four patients, by an association of local and regional flaps in three cases, a temporalis muscle flap in six patients, a lateral pedicled frontal flap in association with titanium mesh in three patients, a lateral pedicled frontal flap in two cases, one medial pedicled frontal flap, one major pectoralis muscle flap and one latissimus dorsi flap. For the patients with lymph node metastasis, lymphadenectomy was performed.

- **Surgical outcomes**

The postoperative results were favorable regarding the complete tumor removal and obtaining an accurate defect closure with a short healing time. The postoperative scars and resulting deformity due to the absence of the orbital tissues could be easily camouflaged by wearing an eye patch.

During the postoperative time there were few local complications that resolved by local and systemic treatment methods. They included partial flap necrosis in three cases, wound dehiscence, and infection in two patients, bone exposure and delayed secondary healing of the exenteration socket in three patients. There was one case of intraoperative cerebrospinal fluid fistula that was managed using a latissimus dorsi flap. Seven patients underwent postoperative radiotherapy. Follow-ups at one month, three months, six months and one year did not show any signs of tumor recurrence.

The positive postoperative outcomes are exemplified by examples of two cases (Fig. 1.4.2.1. - 1.4.2.12.).

Fig. 1.4.2.1. Example 1: Basal cell carcinoma of inferior and superior left lids

Fig. 1.4.2.2. Example 1: Intraoperative aspect after reconstruction of the orbital exenteration defect with a temporalis muscle flap

Fig. 1.4.2.3. Example 1: Postoperative aspect, 3 weeks after surgery

Fig. 1.4.2.4. Example 1: One year after surgery, no clinical signs of recurrence

Fig. 1.4.2.5. Example 2: Recurrence after an operated lower eyelid squamous cell carcinoma.

Fig. 1.4.2.6. Example 2: Clinical signs of scleral invasion

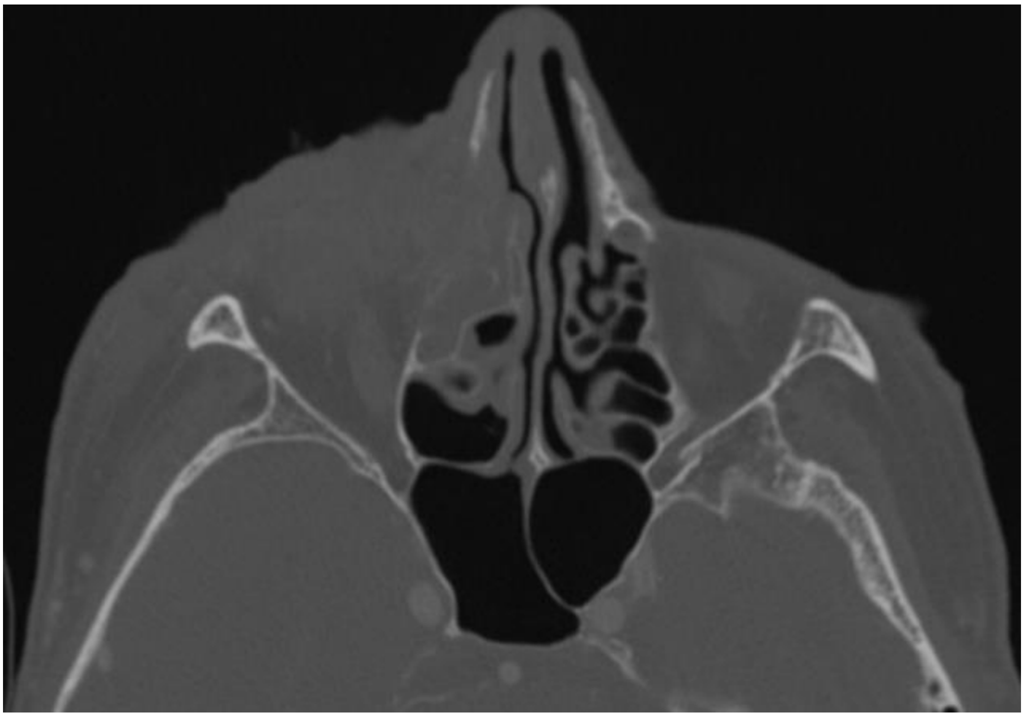

Fig. 1.4.2.7. Example 2: Axial CT section showing orbital invasion with ethmoid extension

Fig. 1.4.2.8. Example 2: Postoperative extended orbital exenteration defect demonstrating the removal of the inferior and internal wall of the orbit

Fig. 1.4.2.9. Example 2: Reconstruction of the defect was made with a median forehead flap

Fig. 1.4.2.10. Example 2: One year after surgery patient presented with a cutaneous dehiscence, without any clinical sign for recurrence

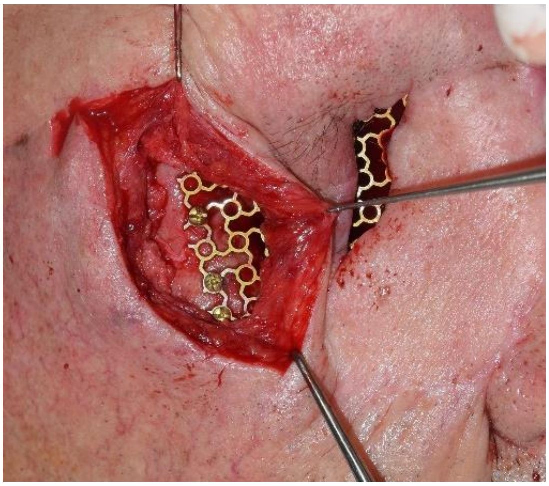

Fig. 1.4.2.11. Example 2: This orifice was closed based on a titanium mesh support fixed on the periorbital frame and covered with soft tissues

Fig. 1.4.2.12. Example 2: The result was stable: postoperative aspect 18 months after correction

1.4.2.3. Discussions

The management of cutaneous tumors with orbital invasion differs regarding the extent of tissue removal in the presence of various patterns of orbital invasion and histologic types. In our study, clinical or radiological evidence of orbital invasion, consisting of tumor tissue extending beyond the orbital septum, into the orbital fat, was an indication for orbital exenteration in all cases to ensure complete tumor removal and decrease the recurrence rate. This is consistent with most of the existing literature on the subject, but there are also authors that suggest a more conservative approach, opting for globe-sparing procedures in anterior orbital invasion from basal cell carcinoma (Catalano et al., 2001; Leibovitch et al., 2005; Madge et al., 2010; Jeancolas et al., 2016).

The slow local invasion and the absence of lymphatic spread, characteristic for most subtypes of basal cell carcinomas, may allow a less aggressive tissue removal. However, basal cell carcinoma in the periocular region is generally associated with more aggressive types considering the growth pattern, such as infiltrative and morpheic (Leibovitch et al., 2005; Meads, Greenway, 2006; Madge et al., 2010). Perineural spread is also exhibited by some histological types and it is a major cause of local recurrence. Additionally, the location of malignancy development in the periocular skin, particularly the medial canthal region and superior nasal-genian fold region favor the deep spread of tumor at the junction of various anatomical elements. Residual tumor may grow extensively before a recurrence diagnosis is made. In consideration of all these factors, we consider advisable to perform an initial orbital exenteration for malignancies eroding through the orbital septum into the orbital fat, regardless of the histology. Complete or partial preservation of an eyelid and conjunctiva can be performed without compromising oncologic safety in most cases, considering the location of the cutaneous malignancy. This aspect is important for obtaining better aesthetic results of the orbital socket reconstruction (Looi et al., 2006).

Although less common than basal cell carcinoma in the periocular region, squamous cell carcinoma is responsible for most cases of orbital invasion that require orbital exenteration procedures (Hoffman et al., 2010). We found similar results in our case series, consisting of 61.1% squamous cell carcinoma cases out of the total.

Malignant conjunctival tumors represent 30% of the conjunctival tumoral pathology (Shields et al., 2017), the most common types being CISCC, melanoma and lymphoid tumor.

All conjunctival carcinomas included in our study were invasive, extending beyond the basal membrane with progressive soft tissue infiltration, late patient presentation and local extension to the orbital structures to various degrees. Conjunctival invasive squamous cell carcinoma usually occurs in elder white patients, mainly those exposed to chronic solar radiation and exposure to cigarette smoke, affecting 5 times more males than females in United States. (Sun et al., 1997). Other predisposing factors include vitamin A deficiency, ocular surface injury and chronic infection with HPV (Human Papilloma Virus) and HIV (Human Immunodeficiency Virus) (Basti, Macsai, 2003; Verma et al., 2008). Ocular surface squamous neoplasia usually presents as a unilateral vascularized gelatinous limbal mass, located in the sun-exposed interpalpebral fissure medially or laterally. Although CISCC rarely metastasizes (less than 1%) (Shields et al., 2017), two of our patients presented intraparotid metastasis at one and respective 6 years after surgery for primary tumor.

The management for CISCC requires surgical removal and/or topical chemotherapy. Topical antiviral medication or photodynamic therapy can also be used in earlier stages (Galor et al. 2012; Shields et al., 2013). Galor stated a rate of recurrence at 1 year of 10 % after surgical removal (Galor et al. 2012). In our cases, the advanced local tumor extension was only suited to complete surgical removal within oncologic safety limits.

Due to its aggressive rapid growth pattern and possibility of lymphatic and hematogenous metastasis, cutaneous periorbital squamous cell carcinoma requires an initial radical resection, involving an orbital exenteration for all malignancies invading beyond the orbital septum. The controversy is regarding lymph node dissection in the presence of a high-risk situation and absence of macroscopic nodes. Lymph node metastases from periocular squamous cell carcinoma may be encountered in up to 25% of cases. Laterally located orbital malignancies drain mostly in the intraparotid and periparotid lymph nodes, while medial tumors drain via the angular and facial vein into the facial and submandibular lymph nodes (Nassab et al., 2007). The same tumor characteristics associated with a higher risk of orbital invasion, are also related to a higher rate of lymph node metastasis for squamous cell carcinoma lesions: increased tumor size, recurrence of previously operated tumors, the depth of invasion, less differentiated histologic subtypes, perineural spread, patient over 70 years of age (Faustina et al., 2004; Thosani et al., 2008). In our study we encountered 2 patients with intraparotid lymph node involvement after at least one year after primary tumor surgery. In the absence of clinically or imaging lymph node involvement, prophylactic lymph node dissection was not considered necessary. This is the general management preferred by most surgeons, although some advocate for sentinel node biopsy in high-risk cases (Nassab et al., 2007; Slutsky, Jones, 2012). With absence of lymph node removal, a careful oncologic surveillance is crucial for the early detection of possible lymphatic metastasis.

Considering the extent of the postoperative defect, several techniques may be used for closure. The simple orbital exenteration socket heals by secondary intention through granulation tissue formation that takes place over three to four months (Tyers, 2006). Covering the socket with a split thickness skin graft can shorten the healing interval. If radiotherapy is planned postoperatively, a good, rapid healing of the socket is desired, thus a local or regional flap may be used. For defects involving the bony walls of the orbit and the neighboring anatomical structures, opening the adjacent sinus cavities (Leibovitch et al., 2005), a regional flap or a free flap is often necessary. Due to the advanced age of the patients and comorbidities, we preferred the covering of the orbital socket using a split thickness skin graft when the orbital walls were intact, without communication with the adjacent sinus cavities. This method allowed shorter surgery time, good results, decreased complications, good oncologic surveillance by direct inspection of the orbital socket, and the possibility to start postoperative radiotherapy. In defects involving the bony walls, we favored the use of local and regional flaps for closure, with good overall results and few complications. Extended defects involving a wide skin surface and a wide opening of adjacent cavities, or associating a cerebrospinal fluid fistula, were closed using a free flap.

Almost one quarter of orbital exenteration procedures are followed by the onset of complications (Tyers, 2006). Studies have found similar complications to the ones encountered in our case series, including exposed bone with prolonged healing of the residual socket, fistula formation and chronic drainage, tissue necrosis and infection, pain (Tyers, 2006). Most complications were managed conservatively, without the need for invasive procedures. We encountered one case of intraoperative cerebrospinal fluid fistula consecutive to the removal of the extended tumor. The closure of the fistula was achieved using a latissimus dorsi flap that was also necessary for covering the remaining skin defect and the exenteration socket.

The main purpose of surgery is achieving local control of the disease and adequate closure of the defect for a rapid postoperative healing, in detriment to the aesthetic result. Secondary procedures can be performed for improving cosmetics (Tyers, 2006; Thosani et al., 2008). An orbital episthesis can be performed to recreate the lost facial features, to decrease the psychological impact of the resulting deformity and increase social integration of the patients. Since the manufacturing of a natural looking episthesis with a good adaptation and comfortable wear is challenging, most patients prefer wearing an eye patch for camouflaging the reconstructed region.

Orbital invasion by CISCC requires the removal of orbital content. The presence of affected regional lymph nodes requires their radical excision (Katz et al. 1988), as it is done in other cases of ocular and periocular tumors with orbital invasion and regional lymphadenopathy (Costea et al. 2013).

In their study, Gichuhi and Sagoo (Gichuhi, Sagoo, 2016) stated that the recurrence rate for CISCC is between 3.2% and 67%, at 32 months average. One patient in this study had a history of conjunctival lesion that was operated and then reappeared, but she could not mention the previous histopathological diagnosis. In this case, CISCC had a long evolution, with corneal, scleral, and orbital fat invasion. Giving the advanced condition of the disease, the enucleation of the eye and partially exenteration of the orbital content was necessary, with the preservation of the eyelids

One of our patients also had a residual corneal leukoma, which led the ophthalmologist to make a differential diagnosis with other lesions of the anterior segment of the eye: cataract, retinal detachment, intraocular metastasis (Turliuc et al., 1997). However, in the cases of CISCC, misdiagnosis and confusion with other conjunctival or eyelid tumors could delay treatment and increase morbidity (Grossniklaus et al., 1987; Goldberg et al., 1993; Char, 1997). Another patient was presented with a poorly differentiated squamous cell carcinoma of the conjunctiva, with deep invasion into ocular structures like cornea and sclera, and also infiltrated the orbital adipose tissue. Enucleation and partial orbital exenteration was indicated in this case of conjunctival squamous cell carcinoma because of the extensive invasion. With the proper surgical excision, the CISCC had a good prognosis with no recurrences at six months after surgery, even in the absence of the oncological treatment.

Concluding remarks

We found that cutaneous and conjunctival malignancies invading the orbit can be adequately managed surgically by orbital exenteration and extended orbital exenteration with good results and few complications. A variety of techniques can be employed for the closure of defects with various extents. The challenges encountered were choosing the most appropriate method for individual defect reconstruction in the presence of comorbidities and advanced age, as well as establishing the opportunity of performing a prophylactic lymph node dissection for orbital squamous cell carcinoma in the absence of clinically or imagistic nodal involvement. Postoperative surveillance is crucial for patients with orbital invasion for the early detection of local recurrence and lymph node metastasis.

1.5. RECONSTRUCTIVE TECHNIQUES IN ORBITAL PATHOLOGY

1.5.1. Reconstruction of defects involving the skin in the orbital region

Despite the superficial growth and facile detection of skin tumors by direct observation and self-examination, epidemiological studies demonstrate a high prevalence of sizeable malignancies with this location (Seretis et al. 2010). Advanced tumor stages upon diagnosis are related to patients often postponing the search for medical advice due to the absence of local pain, the initial unalarming aspect of the tumor, a busy schedule or due to an existing anxiety for the medical personnel and environment (Costea et al., 2013; Sari, 2017). Continuous growth determines local invasion in surface and depth, extension to other regions of the skin, as well as bone and cartilage invasion, that are all enhanced by local inflammation in cases of ulcerated infected tumors (Barro-Traoré et al., 2003; Costea et al., 2014). Thus, it is difficult to obtain correct and complete excision. Furthermore, the reconstruction of the resulting defects is complicated and uncertain from a functional and esthetic point of view. (Adinarayan, Krishnamurthy, 2011; Choi et al., 2013; Apalla et al., 2017a; Eide et al., 2017).

In many cases, because the tumor invades important esthetic and functional units, the radical excision implies important substance loss with resulting deformity and functional impairment, a good example being malignancies located in the periorbital region (Holds, 2008). This area is especially difficult to manage due to the proximity of the orbital contents that may be rapidly engulfed by tumor growth and lead to the necessity to perform orbital exenteration with the resulting sequelae greatly impacting the patient’s well-being. When discussing the surgical ablation of malignancies developing on the face, the preservation of more tissues results in a smoother reconstruction and generally, better aesthetic and functional outcomes (Choi et al., 2013; Eide et al., 2017). Still, the most important aspect that should never be sacrificed in favor of a simple reconstruction, is the complete tumor resection in all planes, certified by tumor-free safety margins. To follow this principle, alongside other reconstructive guidelines particular to the face, such as following the map of aesthetic facial units, the surgeon should be familiar with several reconstructive techniques suitable for different facial regions and different sized defects. A great reconstructive freedom is thus ensured, as well as improved results due to proper reconstruction of the aesthetic units using enough tissue (Fattahi, 2003).

> The results of our collaborative work in this field have been published in the following original article:
>
> - ✓ Tamas C, Pintilie CT, Atanasoae IV, Corduneanu AM, Dabija I, Olaru FS, Hreniuc IM, Tecuceanu A, Munteanu I, Dobre C, Moraru DC, Ianole V, Tamas I, Costan VV. Surgical reconstruction of post-tumoral facial defects. Rom J Morphol Embryol 2018; 59(1):285-291.

The objective of this study was to analyze our results regarding the reconstruction of defects in the orbital and periorbital regions using specific reconstructive strategies, in order to better outline the indications of each technique and improve future outcomes.

1.5.1.1. Materials and method

We conducted a retrospective study including patients diagnosed with malignancies located in the orbital region, as well as neighboring regions, operated between 2015-2018. The tumors were approached in mixed teams, involving maxillofacial surgery, plastic surgery and ophthalmology at times. We noted information including epidemiologic data, the tumor location, histology, the reconstructive method used and the postoperative outcomes, as well as cases where revision surgery was performed. The follow-up was for at least one year after surgery.

1.5.1.2. Results

- **Clinical characteristics**

A total of 54 patients were included in the study, 23 men and 31 women, aged between 32 and 89 years. Histologically, in 45 cases a basal cell carcinoma (BCC) was diagnosed, while the other nine cases were squamous cell carcinomas (SCCs). Malignancies located in the orbital region (29 cases: 24 BCCs and five SCCs) and nasogenian sulcus extended in the orbital region (11 cases, all BCCs) were the most common. Additionally, there were five tumors of the nasal region extended to the orbital region (3 cases BCCs and 2 SCCs), as well as 4 malignancies extended from the zygomatic region (all BCCs), 3 BCCs form the temporal region and two SCCs form the forehead unit extended to the orbital region.

- **Therapeutic approach**

The radical tumor ablation and the defect reconstruction were performed during the same surgery in 52 cases. In two cases the defect healed by secondary intention. Direct closure following tumor excision was performed in 5 cases. In another 5 patients a full thickness skin graft was used for coverage. The skin grafts were harvested from the periauricular region, due to the similar pigmentation and texture, or from the supraclavicular region. In 42 cases, flaps were used for closing the postoperative defect, consisting of 23 pedicled frontal flaps (with median or lateral pedicle), nine temporalis muscle flaps and ten nasogenian flaps. In two cases, the frontal flap was used for coverage of an exenteration defect was associated with titanium mesh reconstruction of the orbital cavity for rendering soft tissue support. The donor site for the frontal flap was closed primarily in all median frontal flap cases and using a split thickness skin graft in lateral pedicled frontal flaps. Three weeks after inset, the pedicle of the frontal flap was sectioned and the tissue in the base of the flap was modelled and rearranged in the donor region. Seven patients underwent further revision surgery for modelling of the inset tissue.

- **Surgical outcomes**

There were no major bleeding or infectious complications following surgery. We achieved good postoperative outcomes in all cases regarding adequate defect closure. There postoperative appearance was good in cases that did not necessitate orbital exenterations and acceptable in the other cases. Eyelid function was adequate after surgery in the majority of patients. There were 3 cases of postoperative inferior eyelid ectropion that necessitated further revision surgery. There were no recurrences at one-year follow-up.

In the cases where it was necessary to include the subjacent bone in the surgical specimen, because of the missing hard tissue support under the flap, we wanted to avoid the onset of postoperative wound dehiscence, by using from the beginning a titanium mesh under the soft tissue used for reconstruction. This allowed rendering contour to the region and offer support for the repositioned soft tissues (Fig. 1.5.1.1. – 1.5.1.8.).

Fig. 1.5.1.1. Patient with basal cell carcinoma from zygomatic region extended in left orbit

Fig. 1.5.1.2. Intraoperative aspect after extended orbital exenteration with removing of the floor of the orbit and inferior border of the orbit

Fig. 1.5.1.3. Reconstruction of the bony defect was made with titanium mesh

Fig. 1.5.1.4. Soft tissue reconstruction was made using a temporal flap and a forehead flap with lateral pedicle

Fig. 1.5.1.5. Temporal flap was passed into the orbit through the lateral wall of the orbit

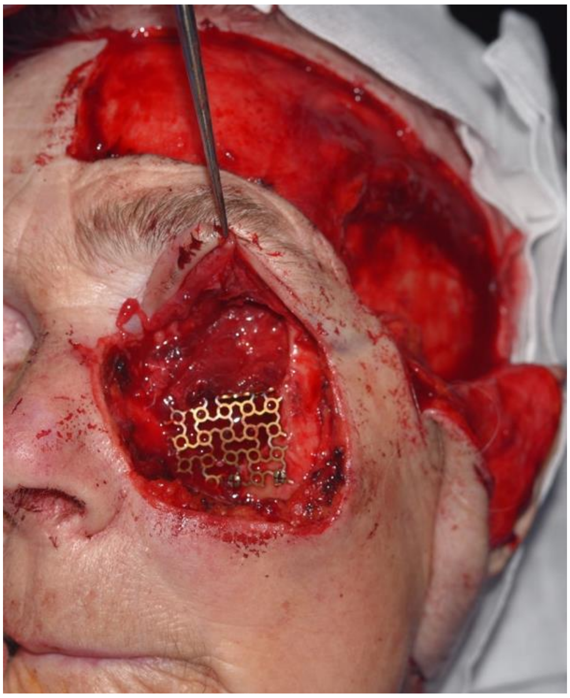

Fig. 1.5.1.6. Intraoperative aspect after reconstruction with temporal flap

Fig. 1.5.1.7. Aspect immediately after reconstruction with a forehead flap

Fig. 1.5.1.8. Postoperative aspect after one year, showing a good and stable appearance

1.5.1.3. Discussions

In managing skin malignancies, the reconstructive surgeon must follow the oncologic principles regarding tumor excision with safety margins, while also ensuring proper defect closure for defects of various thickness and composition, involving different anatomical regions. Tumors located on the face are especially challenging to reconstruct, since this is the most important anatomical area for patients regarding appearance and influencing social aspects (Hajdarbegovic et al., 2009).

Repairing a post-excisional soft tissue defect requires functional restoration of the area concerned, as well as the appearance in the damaged area. In his reconstructive efforts, the surgeon is supported by the use of an algorithm provided by the reconstructive scale in evaluating defect coverage. This means soft tissue thickness assessment in the damaged area and the exposed tissue guides the treatment, which consists of excision and direct suture, followed by skin grafts or local flaps (Tiutiuca et al., 2016).

Clinically, tumor aggressiveness can be assessed by following its patterns of invasion and assessing aspects such as ulceration (Newlands et al., 2016; Apalla et al., 2017b). Skin grafts offer the advantage of better long-term monitoring of the region, especially for tumors associated with a high risk of local recurrence and inflammation. However, for various tumor locations and invasion of the deep structures, including cartilage and bone extension, requires a wider and more profound excision. The skin graft is obviously not suitable as an option for reconstruction in such cases, thus flaps must be considered for adequate coverage of the deep tissues. Furthermore, local flaps offer better long-term results, especially from an esthetic and functional point of view, for facial soft tissue defects (Hajdarbegovic et al., 2009).

The most common histologic type of tumor in our retrospective study was BCC. Our findings are similar to the existing literature data stating that BCC is the most common malignant tumor in the skin, within 70-80% of encountered cases (Mantese et al., 2006). Its general population occurrence percentage is 4 to 5 cases of BCC for every SCC case and 8 to 10 cases of BCC for each newly diagnosed melanoma (Mantese et al., 2006). There has recently been an increase in the incidence of BCC worldwide, probably related to sun exposure (Mohan, Chang, 2014).

The results of our studies confirm that there is a high occurrence of BCCs in elderly patients with respect to the histological tumor types, whereas melanomas are more common in younger patients. We also found BCCs in younger patients. Of the 51 patients diagnosed with facial skin malignancies, the majority were over 55 years of age. This result is consistent with literature studies where over half of cases occur between the ages of 50 and 80 (Kopke, Schmidt, 2002).

There is a strong correlation between the ultimate histological diagnosis and long-term surgical strategy planning. In the event of late local and regional tumor recurrence, it is preferable to start by choosing the option of local small flaps to save the more distant and complex reconstructive techniques as a last solution (Newlands et al., 2016; Apalla et al., 2017b; Chinem, Miot, 2011).

The BCC predominates in our study, and although exposure to UV radiation has been shown to be the main risk factor associated with this tumor genesis, the correlation between sun exposure patterns, patient age, and histological aggressiveness is still subject for debate among researchers. Further epidemiological and anatomopathological studies involving different population groups are therefore needed for clarity. Studies have shown that BCC occurs most frequently on sun-exposed areas of the skin, with 80% of cases on the face and only 15–43% on the trunk (Chinem, Miot, 2011). BCC may occur from ten to fifty years after damage produced by the sun (Roewert-Huber et al., 2007). Autoimmune conditions may also promote skin cancer development (Chaudhary et al., 1994; Lanoy, Engels, 2010; Buzdugă et al., 2017).

BCC may have a variety of macroscopic aspects, ranging from erythematous plaques to pigmented lesions, making histopathological examination compulsory to establish a certain diagnosis. BCC is characterized in microscopic examination by proliferation of tumor cells with small oval and hyperchromic nuclei and small cytoplasm in the form of nests or strands. Neoplastic cells in appearance are relatively uniform and have significant anaplasia and mitotic figures at times. They are usually arranged in a radial pattern at the border of the nests, called "palisading." While this does not permit the establishment of a definite diagnosis, the diagnosis of basal cell carcinoma should be questioned in its absence (Sava et al., 2015). Regardless of their size or cell arrangement, basal cell carcinomas have the same type of cell. All identical basophilic tumor cells resemble the epidermis ' basal cells, hence the name of basal cell carcinoma, but they are in fact undifferentiated epidermal tumor cells. They are elongated, with dense chromatin having an oval or elongated nucleus; the cytoplasm is very low, often poorly defined. Mitoses vary in frequency from tumor to tumor (Sava et al., 2015). Although typical cutaneous BCCs and SCCs are morphologically dissimilar, it is well known that poorly differentiated SCC may assume a basaloid phenotype, making it difficult to distinguish histologically between these two tumors (Webb et al., 2015).

Tumors that develop in the squamous layer of the epidermis, pierce the dermal-epidermal basal membrane and lead to dermis invasion. Microscopically speaking, atypical squamous epithelial cells with reduced eosinophilic cytoplasm and hyperchromic nuclei with numerous atypical mitoses, acanthosis, parakeratosis and dyskeratosis have strands or nests (Older, 2003; Sava et al., 2015). Inflammatory infiltrations are shown by fibrovascular stroma. For accurate microscopic diagnosis, histopathological and IHC (Immunohistochemistry) examination are very important. For all SCC and malignant melanoma cases, IHC examination was absolutely necessary in our study.

We preferred median forehead flaps due to their satisfactory coverage potential and proximity to the recipient region in cases requiring the reconstruction of internal canthus defects. In addition, the morbidity of the low donor site provides the best functional and esthetic results.

Fortunately, BCC is usually early diagnosed and treated (Alam et al., 2011). As long as it is diagnosed early (18% of our BCC group), BCC exhibits only local invasive behavior and has low metastatic potential, being easily treated by surgical excision (Chinem, Miot, 2011). Nevertheless, BCCs may become "advanced BCCs" in two cases: when patients neglect the tumor and when BCCs are intrinsically aggressive and recur, or are refractory to treatment (Mohan, Chang, 2014).

Skin cancers most frequently affect heavily sun-exposed areas of the face: orbital region, nasogenic region and nasal regions, zygomatic region, suggesting the important role of UV light exposure (Franceschi et al., 1996; Leiter, Garbe, 2008). In our case series, basal cell carcinomas were most often located in the orbital region and the nasogenian fold. High-impact facial areas with complex anatomy require different coverage techniques to restore local anatomy, function and appearance when possible (Tiutiuca et al., 2016). In this regard, the excision for BCC with facial location was determined by the proximity of the initial tumor with important orbital structures. The only guide for a correct surgical protocol in this particular situation is the histological result. Furthermore, we find that preoperative biopsies are not only irrelevant in such specific cases, but also dangerous for a positive long-term evolution; excision with limited margins followed by histological examination is a better option. We considered that extension of the malignancy into the orbital fat is an indication for performing orbital exenteration.

Numerous orbit invading tumors requiring orbital exenteration involve the reconstruction of the orbital cavity or of the periocular region (Turliuc et al., 2015; Costea et al., 2017c; Sapte et al., 2017). In this regard, we obtained favorable outcomes using the temporalis muscle flap for orbital socket coverage. Restoring the support for the soft tissues is another issue of concern in reconstructive surgery, as demonstrated by our case of cutaneous dehiscence that was solved by inserting a titanium mesh for supporting the overlying soft tissues.

Concluding remarks

Periorbital skin defects are especially difficult to reconstruct, due to the desire to restore eyelid function and protect the orbital contents. The characteristics of the skin in the region are also not easy to match. Sequelae involving eyelid mispositioning are common and require additional refinement procedures. The proximity of the orbital contents predisposes to malignancy breaching into the orbital fat and the need for orbital exenteration.

Nevertheless, as demonstrated by our study, with proper assessment of the defect characteristics, as well as defining the reconstructive goals, the most suitable option for the restoration of each individual defect is achieved, with optimal postoperative outcomes regarding form and function.

1.5.2. Reconstruction methods for extended defects involving the orbit and the skull base

The orbit is frequently involved by malignancies spreading from neighboring structures, due to its close anatomical relation to the infratemporal fossa, paranasal sinuses, and the skull base. Tumors arising in any of the previously mentioned regions are diagnosed late, due to the absence of clinical signs until the later stages of tumor evolution (Richmon et al., 2015). This is due to the deep location of the anatomical structures involved. Compound defects involving the orbit and the skull base are especially difficult to manage due to the established direct communication of the intracranial space with the exterior and the scarcity of local soft tissues and vasculature available for reconstruction. Frequently, an association of techniques is necessary for achieving adequate closure. A mixed multidisciplinary team is necessary in the management of such extended tumors, due to the involvement of multiple anatomic regions, difficult access and the necessity for complex reconstructive procedures (Marzo et al., 2011; Neel et al., 2017; Vogt et al., 2017).

The prognosis and the survival of a patient with a cranio-facial malignancy is very often directly related to the extent of the necessary resection. Extensive ablation procedures lead to impressive cosmetic and functional deficits resulting in a high psychological impact, as well as severe consequences on the patient's quality of life. In most cases the ablative surgery implies the removal of large amounts of tissues and a complex reconstruction will be necessary. There are plenty of reconstructive methods to choose from, depending on the surgeon's experience, varying from the different types of skin grafts to local, regional and distant flaps, as well as the use of various other autogenic materials, but also alloplastic, allogeneic and xenogeneic materials (Richmon et al., 2015; Vogt et al., 2017).

We present our experience emphasizing the importance and the reliability of local, regional, and distant flaps, as well as various synthetic materials in cranial base reconstructive surgery. The temporalis muscle flap is an axial flap, providing very well vascularized tissues, located in the proximity of the reconstruction site, easy to tailor and manipulate and rendering satisfactory results (Spanio di Spilimbergo et al., 2017). The pectoralis major musculocutaneous flap is another quite versatile regional flaps, that can reach distant areas and can be used for reconstructing tissue defects of the pharynx, larynx, oral cavity, neck but also, craniofacial defects (Teo et al., 2013). For extensive defects involving several tissue layers, free flaps may provide enough tissues for reconstruction while not having the disadvantage of modifications associated with the presence of a pedicle (Vogt et al., 2017).

By working in multidisciplinary teams, we were able to improve the surgical treatment and reconstruction methods for patients presenting with extensive cranio-facial malignancies. Part of the results of our work were published in the following manuscript:

- ✓ Dabija M, Boisteanu O, Dorobat V, Dargomir R, Ibric V, Costan VV. Reconstruction of skull and skull base defects using titanium, collagen, polyesterurethane and other alloplastic, allogeneic, xenogeneic and autogenic materials. Rev Chim 2018; 69(5):1276-1278.

The purpose of the study was to review our experience in using various reconstructive methods, tissues and materials for craniofacial defects involving the skull base and orbit, following tumor resection surgery.

1.5.2.1. Materials and method

We reviewed the medical records of patients who underwent surgery for malignant tumors involving the orbit and the skull base in between January 2012 and November 2018. The procedures were performed in mixed teams involving maxillofacial surgery and neurosurgery. The included patients had minimum six months of follow-up.

1.5.2.2. Results

- **Clinical characteristics**

We identified 14 cases of extended defects involving several regions, including the skull base (14), orbital content (2), or orbital walls (12). The initial starting point of the malignancy was the skin in the auricular region (1), the temporal region (4), the frontal region (5), the intracranial tissue (1), distant metastasis (2), recurrence of temporo-mandibular joint malignancy (1). There were seven basal cell carcinomas, five squamous cell carcinomas, one sarcoma and one meningioma. From the total number of patients, there was only one woman. The age of the patients was between 46 and 83 years old.

- **Therapeutic approach**

The plasty of the defects was performed by use of three local rotation flaps, six temporalis muscle flaps, three great pectoralis musculo-cutaneous flaps and two latissimus dorsi flaps. In four cases, the muscle flaps were used in association with local flaps for improved defect closure. In three cases, synthetic materials were used for closure of the dura mater, while in another two cases, titanium mesh was necessary for rendering support and protection for the intracranial space.

- **Surgical outcomes**

Defect closure was adequately achieved in all cases of flap reconstruction ensuring proper separation of the anatomical cavities. Both the muscular flaps and the association of local flaps and synthetic substitutes were efficient in the isolation of the intracranial space by achieving dural closure. The temporalis muscle, the pectoralis major (Fig. 1.5.2.1. – 1.5.2.8.) and the latissimus dorsi flaps (Fig. 1.5.2.9. – 1.5.2.12.) were equally efficient for the isolation of the neurocranium, but the pectoralis major and latissimus dorsi flaps initially offered more volume useful for improved obliteration of the dead space in the presence of more extended defects.

There were no postoperative occurrences of cerebrospinal fluid fistulas or intracranial space infections. The outcomes regarding facial appearance were satisfactory. Minor postoperative complications involved hematoma formation, marginal necrosis of the skin paddle of the greater pectoralis muscle flap and wound dehiscence, without exposure of the intracranial space.

Fig. 1.5.2.1. Example 1: Patient with an extended basal cell carcinoma involving the temporal and parietal bones, extended into the orbit - frontal view

Fig. 1.5.2.2. Example 1: Patient with an extended basal cell carcinoma involving the temporal and parietal bones, extended into the orbit – half-profile view

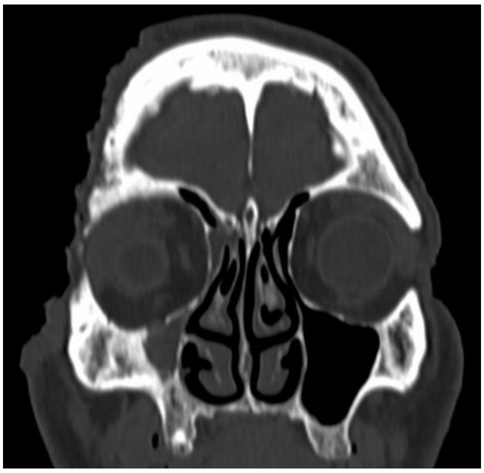

Fig. 1.5.2.3. Example 1: CT aspect in the coronal view, showing the bone and orbit invasion by the tumor

Fig. 1.5.2.4. Example 1: Aspect in the sagittal view, with bone and orbit invasion by the tumor

Fig. 1.5.2.5. Example 1: Intraoperative aspect of the defect following the extended right orbital exenteration with partial skull vault resection

Fig. 1.5.2.6. Example 1: Intraoperative aspect after a pedicled pectoris major flap reconstruction

Fig. 1.5.2.7. Example 1: Frontal aspect after one year

Fig. 1.5.2.8. Example 1: Half-profile aspect after one year

Fig. 1.5.2.9. Example 2: Patient with recurrent squamous cell carcinoma from the eyelid, extended in the right orbit. The patient is also known with neurofibromatosis, with the presence of characteristic cutaneous lesions.

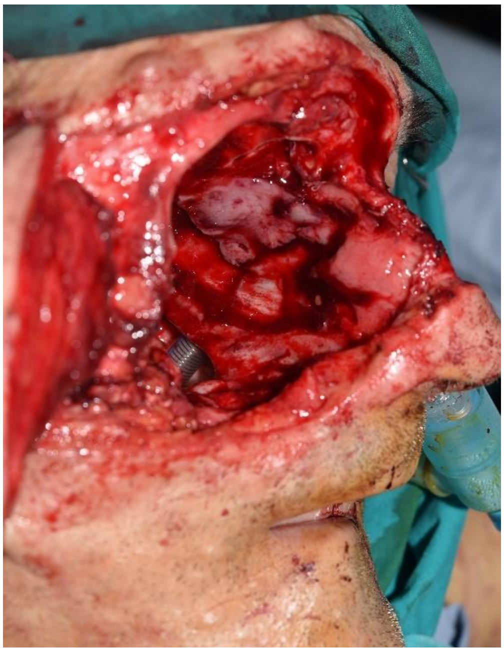

Fig. 1.5.2.10. Example 2: Intraoperative aspect after orbital exenteration with opening of the anterior cranial base

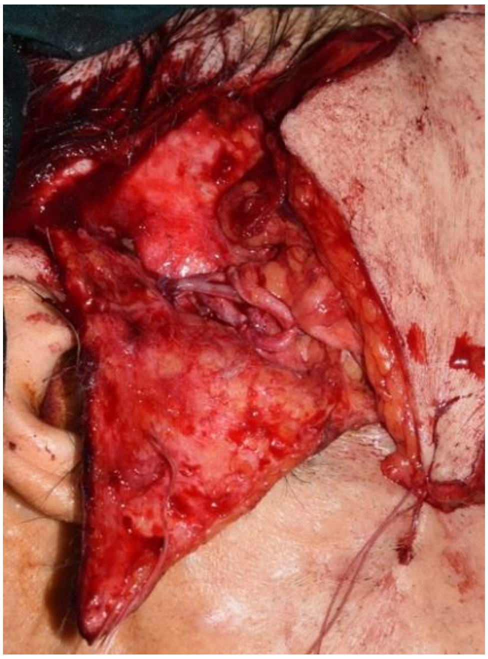

Fig. 1.5.2.11. Example 2: Intraoperative aspect after micro-anastomosis between pedicle of the latissimus dorsi and superficial temporal vessels

Fig. 1.5.2.12. Example 2: Six months postoperative aspect

1.5.2.3. Discussions

The management of extended tumors involving the skull base and the orbit is quite challenging, regarding both the resection and the reconstruction. Composed defects involving bone, soft tissues and opening the intracranial space require complex methods of reconstruction for achieving separation of anatomical spaces and avoiding infectious postoperative complications. The aesthetic outcome is not a priority in such extended malignancies, but wide tumor removal and accurate closure of the resulting defect are necessary for decreasing complications, increasing survival and offering a satisfactory quality of life (Marzo et al., 2011; Vogt et al., 2017).

Choosing the most appropriate method of reconstruction depends on the location, extent, depth and composition of the defect, but also on the preference and personal experience of the surgeon, as well as the existing equipment and experienced staff (Maier et al., 2009). In our study, the preferred method of defect closure was decided according to the amount of missing soft tissues and bone, considering in the first place to firmly isolate the intracranial space and reduce the occurrence of complications. The aesthetic outcome was less of a concern, while oncologic safety and function preservation were the primary focus of the surgery.

The decision of performing an orbital exenteration is another important matter in the presence of tumors invading the orbital bony walls, due to its psycho-emotional impact on the patient (Vogt et al., 2017). In our case series, a decision of removing the orbital contents was taken when there was proof of tumor extension beyond the orbital periosteum, into the orbital fat. If the invasion involved only the orbital bone, without breaching the periosteum, a bony resection was performed, with conservation of orbital structures. Still, it is advisable to obtain a written consent for exenteration before surgery in all instances, since intraoperative diagnosis of more extensive invasion than demonstrated by imaging is not a rare encounter.

Dura mater integrity is a major concern in the resection of large, aggressive, locally invasive carcinomas, due to the possible debilitating life-threatening complications that may occur postoperative. The infiltration of the meningeal layers is quite commonly noticed during surgery and the radical resection is made with the assumed cost of a dural defect. When this occurs, in conditions of communications with septic anatomical regions, such as the nasopharynx, the paranasal sinuses and the mastoid, there is a high risk of ascending infections and severe postoperative meningitis. Therefore, it is mandatory to achieve the closure of dural defects whenever possible and to isolate cranial and facial compartments by a properly designed, adequately sized, healthy and well vascularized barrier, represented by musculocutaneous flaps (Marzo et al., 2011; Neel et al., 2017). In our experience, we managed to repair the existing dura mater defects using autologous tissues in the form of local, regional, or distant flaps. We also achieved positive outcomes by using local flaps and synthetic dural substitutes placed in a layered fashion.

Defects that involve the nasal cavity, the frontal, sphenoid and ethmoid sinuses have an increased risk of infection especially when the dura and subarachnoid space is open. The type of surgery in these cases can be considered as clean-contaminated (Gil et al., 2003). In our patients we, in cases, in which we opened nasal or sinus spaces and intracranial compartment, we preferred at least 7 days of antibiotic treatment and we didn’t notice any major infectious complication.

Voluminous skin and bone defects imposed the use of large soft tissue flaps for obtaining closure. The pectoralis muscle pedicled flap is reliable in covering a wide surface, while also providing volume due to the muscle mass. It can also be rotated to reach defects as far as the parotid, auricular and temporal regions. Although a reliable flap for various types of defects, the pectoralis muscle flap is not without downfalls (Vogt et al., 2017). One disadvantage is that the initial aspect is not preserved over time, due to the gradual decrease in volume because of muscle atrophy (Marzo et al., 2011). Another important issue is the marginal flap necrosis that sometimes happens during the normal healing period. It is essential to adequately place these flaps so that a potential flap necrosis does not compromise the sealing of the neurocranium. In such an occurrence, the plasty can be easily performed using skin grafts or local skin flaps. In one of the cases included in our review, even in the presence of a large surface defect, a skin graft was preferred for coverage due to the patient's advanced age and the need for a short surgery time. This was possible because part of the temporalis muscle was preserved, as well as the periosteum.

Another issue is adequately positioning the muscle flap for closing or filling postoperative defects that open cavities of the facial skeleton (Chiu et al., 2008). In two of our patients, invasion of the orbital contents dictated the need for performing orbital exenteration. In addition to skull or skull base defect closure, the muscle flap was also used for filling of the orbital socket. The temporalis muscle flap is particularly useful in this regard, considering the proximity to the defect site.

The choice of reconstructive material should carefully consider the characteristics of the defect regarding, size, shape, the type of missing tissue and the condition of the surrounding tissues. Autologous materials including connective tissue grafts can be used for closing dura mater defects, but this is depended on the size of the defect and the availability of regional tissue for harvest, as well as consideration for the morbidity of a second harvesting site. Another option is the use of allogeneic graft materials, such as "lyophilized" dura mater, but the incidence of transmitted viral infections proved to be high in several studies using this technique (Maier, 2009; Marzo et al., 2011). Xenogeneic materials, such as collagen membranes of porcine or bovine origin, coated or not with fibrin polymerization enhancing agents, are maybe the most used for achieving dura mater closure, with good results related to obliteration and biocompatibility, explained by the structure of the dura which is mainly composed of Type 1 collagen. Alloplastic materials in the form of degradable (Polyglactin 910, poly-P-dioxanon, polyesterurethane) and non-degradable (nylon, Dacron, silastic) sheets can also be considered for dura mater defect obliteration (Maier, 2009).

There is a wide variety of alloplastic materials available for reconstruction. We consider their implementation useful for the plasty of dura mater defects– Neuro-Patch, Duragen, but also for the reconstruction of bone surfaces, such as skull defects, where titanium mesh provides defense from traumatisms. Neuro-Patch is a fine fibred structure made by a highly purified polyesterurethane and Duragen is a type I collagen-based structure from bovine Achilles tendon in which the precise porosity of the material allows that fibroblasts to integrate the patch to the endogenous dura mater. Both dural substitutes have high liquid tightness, good tissue tolerance, high tensile strength for good suturability, very good elasticity to make them adaptable to the anatomic conditions (Maier, 2009). Duragen will be fully resorbed and replaced by native tissue and even the sutures are not always required, in our case we used tensionless stay sutures for a better placement of the patch. In our study, synthetic materials were useful in certain cases of neurocranial defects for providing protection with overall good results. Adequate indication and proper technique increase the rate of success in closing dural defects using synthetic materials.

Bone defects involving the frontal or temporal skull can impose additional reconstruction methods for providing shape and mechanical resistance and protection of the intracranial structures. Alloplastic materials can be especially useful in providing form and strength while eliminating the need for bone graft reconstruction that would be limited, considering the shape and extent of the defect, as well as additional donor site morbidity (Liu et al., 2004). The alloplastic materials available for hard tissue reconstruction include bioactive glass ceramics, cements (Polymethylmethacryl-PMMA bone cement, hydroxyapatite cement), composite materials (carbon-fiber polymers and an epoxy resin matrix), plastics (porous polyethylene, polyetheretherketone) and most importantly- metals (Titanium mesh) (Maier, 2009; Richmon et al., 2015). We prefer using titanium mesh for its chemical properties and resulting mechanical characteristics. Since pure titanium (under one percent additives) production is a complex procedure, other elements are found in association with titanium, producing alloys that are generally available in commercial osteosynthesis titanium meshes or plates, with the chemical structure of Ti-6Al-4V (6% aluminium and 4% vanadium) or Ti-6Al-7Nb (6% aluminium and 7% niobium) (Neumann, Kevenhoerster, 2009; Maier, 2009). A titanium oxide layer forms at the surface of the material, contributing to both corrosion resistance and biocompatibility due to glycoprotein adhesion. It's corrosion resistance, biocompatibility, the elasticity modulus above the one of human bone (105 kN/mm2), the light mass and high stability, are the main properties that make titanium a very appropriate material for hard tissue reconstruction (Neumann, Kevenhoerster, 2009). Titanium mesh, due to the supplemental characteristics rendered by the pattern and structure of the panel, is particularly useful for skull base reconstruction. It offers the possibility of simple shaping, while also providing the increased strength necessary for the protection of intracranial structures. Another advantage is the possibility of intraoperative modelling of the mesh as well as the possibility of using computer aided shaping (Luo et al., 2012).

Among the useful materials for craniofacial reconstruction, titanium mesh provides adequate structural support and it is easy to shape and contour. Additionally, it ensures a good tissue coverage, is biological inert, has a good resistance and durability, and is associated with a low infection rate (Liu et al., 2004). Another advantage is that it is safe for further survey using MRI. In two of our cases, we used cranioplasty techniques using titanium mesh. We achieved positive outcomes in situations requiring mechanical reinforcement for improved brain protection and for satisfying cosmetic results. In addition, cranioplasty has a favorable effect on cerebral metabolism and facilitates rehabilitation (Winkler et al., 2000). It also prevents movement of the soft tissues used for lining of the cutaneous defect. This mobility in proximity of the brain tissue is highly unpleasant for the patient and it impedes the proper healing of the tissue.

Defects involving several tissue layers, including the dura mater, bone, soft tissues, and skin, impose careful evaluation of the choice of material and reconstructive technique. The main purpose of reconstruction is achieving a tight closure of the intracranial space (Maier, 2009; Marzo et al., 2011). We consider that this desiderate is achievable in composite craniofacial defects by performing a layered closure using collagen or polyesterurethane membranes for dura closure, together with regional muscle flaps for dead space obliteration, ensuring tissue volume, but also skin defect closure where needed. In our experience, titanium mesh reconstruction of fronto-temporal bone defects provides excellent protection of the intracranial structures. Additional sequelae of the extensive cranio-facial resection procedures, such as facial nerve paralysis sequelae, can be addressed in subsequent surgical appointments.

Concluding remarks

In our experience, local, regional, and distant flaps are useful for the plasty of extended cranio-orbital defects, rendering acceptable appearance and good separation of anatomical spaces, when designed and used appropriately, in accordance with the structure of the defect. Muscular flaps, as well as synthetic materials are efficient in closing dural openings and preventing intracranial complications. Titanium mesh reconstruction is a valuable method of restoring lost bone contours, in order to provide support for the overlying soft tissues and protect underlying structures. A multidisciplinary approach is necessary for the management of such complex cases, in respect of access, tumor resection, reconstruction and follow-up.

CHAPTER 2.
ADIPOSE TISSUE IN ORAL AND MAXILLOFACIAL SURGERY

Adipose tissue is the current focus of many research studies attempting to better define its roles as a structural and functional tissue in the composition of different anatomical segments. An increased understanding of its properties contributes to crucial developments in the area of regenerative medicine and reconstructive surgery, with multiple and expanding clinical applications (Fontes et al., 2018; Riesco et al., 2018).

Autologous fat grafting (also named autologous fat transplant, structural fat grafting, lipostructure, lipofilling and lipografting) is a procedure that involves harvesting the fat using special cannulas, processing it by centrifugation and then injecting it at the level of deficient regions. The benefits of lipografting are rendered by the main properties of the fat, consisting mainly of filling and regenerative features (Coleman et al., 2018; Romeo, 2019).

2.1. STATE OF THE ART IN AUTOLOGOUS FAT GRAFTING

2.1.1 Fat structure and biology

The fat tissue within the anatomical layers of the body greatly contributes to heat insulation and thermogenesis. They also provide mechanical protection for the organs they contain. In the head and neck region, the mechanical role is most obvious in the orbital fat that forms a protective cushion around the globes (Rosen, Spiegelman, 2014). Additionally, the facial fat pads allow the sliding of the soft tissues, ensuring the required mobility for the mimetic muscles in rendering facial expression (Cotofana, Lachman 2019).

Two main types of fat tissue exist in the body- white adipose tissue and brown adipose tissue, although recent studies also described the presence of beige adipocytes, exhibiting features pertaining to both brown and white adipose cells (Cannon, Nedergaard, 2004; Wang, Seale, 2016). The brown fat is characterized by adipose cells containing multilocular lipid droplets and numerous mitochondria. A protein found in the inner mitochondrial membrane of brown adipose cells, the Uncoupling Protein-1 (UCP-1), is responsible for the main function of this subtype of fat, which consists of stored energy dissipation in the form of heat. The main anatomical locations of brown adipose tissue have been described using PET (positron-emission tomography) imaging. It is mainly found in the paracervical and supraclavicular regions (Virtanen et al., 2009). Some authors have underlined the high histologic similarity between the Bichat's fat pad and the visceral adipose tissue (Bertossi et al., 2015).

The white subtype forms the majority of the body fat and it is also the type that is currently utilized in autologous fat grafting. It contains large adipose cells with a single lipid droplet, and less numerous mitochondria than the brown subtype. The origin of the facial white adipose tissue is the neural crest (Billon et al., 2007), different from the rest of the white fat which derives from the mesoderm (Rosen, Spiegelman, 2000). The white adipose tissue is structured into two main anatomical layers- the subcutaneous fat and the visceral fat (Zwick et al., 2018). The commitment and differentiation of the adipocytes in the subcutaneous adipose tissue take place in the second trimester of pregnancy and their number remains stable in the postnatal life, while the visceral fat adipocytes preferentially differentiate postnatally (Wang et al., 2013).

The adipose tissue contains within its structure cells, blood vessels, lymph nodes and nerves, comprised in an extracellular matrix with collagen fibers of different types. Inside the cellular component we encounter stromal-vascular cells, and mature adipocytes. The latter make up approximately 90% of the fat volume, but merely 20-40% of all fat cells, while 60-80% of the fat cells are stromal-vascular cells (Rosen, Spiegelman, 2014). Due to their increased volume, the mature adipocytes are responsible for the filler effect of the adipose tissue. Other properties of mature adipocytes have been noticed in the enhancement of wound healing in which they actively participate, since their presence is required for fibroblast recruitment during the reconstruction of the dermis. Additionally, mature adipocytes help protect against invasive skin infections involving Staphylococcus aureus, by releasing an antimicrobial peptide- cathelicidin (Zhang et al., 2015). They also contribute to the regeneration of skeletal muscles by secreting adiponectin, among many other adipokines (Fiaschi et al., 2014). More than half of the fat contained stromal-vascular cells are leukocytes, while the other half is represented by pre-adipocytes, endothelial cells, pericytes, fibroblasts and the adipose-derived stem cells (ASCs) which render the regenerative features of the adipose tissue due to their possible differentiation into multiple cell types. The adipose-derived stem cells also have immunomodulatory and trophic effects on several tissues, properties that are attributed to the ASCs' secretome comprising multiple growth factors, adipokines and interleukins.

2.1.2 Anatomy of head and neck fat

To better define the level of deposition of the adipose tissue during autologous fat grafting, the surgical anatomy of the face is best described in tissue layers. In between the skin and the periosteum, two main fat layers are encountered in the face, the superficial subcutaneous fat and the deep fat, separated by the superficial musculoaponeurotic system (SMAS). This is a general disposition of the tissue layers to allow a comprehensive overview but it should be adapted in certain regions of the face where more numerous layers can be identified, like the temporal region (Kruglikov et al., 2016; Cotofana, Lachman 2019). The two fat compartments disposition is also continued in the cervical region where the superficial and deep fat layers are separated by the platysma muscle (Larson et al., 2014).

The facial ligaments play a definite role in the segmentation of the described fat compartments, and in the soft tissue arrangement, particularly in the midface, with consequences on the outcomes of facial filling procedures in relation to the location of the filler injection lateral or medial to the ligament line. This described ligament line extends from the temporal crest to the mandible and represents the projection of all major facial ligaments- the temporal ligamentous adhesions, the lateral orbital thickening, the zygomatic ligament and the mandibular ligament (Cotofana, Lachman 2019). The clinical significance of this line in relation to autologous fat grafting resides in the injection outcomes. Administering the fat lateral to the line results in lifting of the inferiorly located soft tissues, while injections located medially cause more projection of the soft tissues (Cotofana, Lachman 2019).

2.1.3 Techniques of fat harvesting and processing

Over the course of time, different techniques of autologous fat grafting were used, regarding the sampling, the processing and the grafting of the adipocytes at the level of the receiving areas, in order to increase the chances of local integration and preserve the properties of the harvested fat (Fontes et al., 2018).

Grafting adipose tissue to correct the soft parts in the maxillofacial area was first used and described over 100 years ago by Neuber, in his search for an ideal natural material (Bagheri et al., 2018). By harvesting blocks of adipose tissue from the abdomen, the author carried out a fine correction of volume deficits in the cephalic extremity. In 1912, Hollander underlines and reports the facial modifications that follow fat infiltration in patients with facial lipoatrophy. A step forward is taken in 1926 by Miller, who published data based on his own experience regarding fat injection, using his own cannulas. This technique represented a huge advancement compared to the harvesting of fat tissue blocks and was somewhat similar to the technique of autologous fat grafting, the essential difference being that the harvested material was not centrifuged before injection (Mazzola, Mazzola, 2015). However, those attempts were later abandoned, because the excellent initial results were lost as time passed, the final outcomes being, at times, even worse than the situation before the grafting. The degradation of the results was due to the volume of the fat graft that did not allow for its quick revascularization and therefore, the adipocytes became necrotic in the center of the graft, leading to fibrosis and sometimes to significant retractions at the level of the receiving area.

These deficiencies were later corrected by Sydney Coleman who, at the end of the 1980s, developed a new technique of sampling and processing the fat, called autologous fat grafting, used in plastic surgery for redefining the facial contour and creating a well-proportioned facial harmony (Coleman, 1995). Sampling the fat through cannulas and then centrifuging it allowed the preparation of a material made up only of viable adipocytes, easy to use. The same principles are still used to the present time, although the harvesting instruments, pressure, as well as the time and intensity of centrifugation are constantly adapted by different authors in an attempt to maximize the viability and preserve the characteristics of the grafted fat.

Autologous fat grafting offers an optimal solution to restoring facial symmetry and increasing the comfort of the patients by improving the quality of the tissues and decreasing pain. The constant upgrading of the harvesting protocols for maximizing the benefits of lipofilling is still the current focus of many studies (Fontes et al., 2018).

Large fat depots in the body are found in the inferior abdomen, the gluteal regions, the inferior side of the upper thighs and the lateral femoral regions, which are the preferred sites for harvesting adipose tissue. If the percentage of body fat is low, ultrasound may help locate the areas of increased thickness before fat harvesting (Shim, Zhang, 2017). Although differences have been found in the structure and characteristics of fat harvested from different sites, in view of connective tissue amount, density of adipose-derived stem cells, adipocyte size and enzyme activity, the impact of such differences on the outcome of the fat grafting procedure could not be proven (Simonacci et al., 2017). The actual fat harvesting can be performed under general or local anesthesia by either existing the fat surgically, by performing vacuum liposuction or by using a cannula and syringe under manual aspiration (Kakagia, Pallua, 2014; Fontes et al., 2018). The last method is generally preferred for reconstructive purposes, since it does not imply obvious scars and is less traumatic than the vacuum suction, with less adipocytes being destroyed (Pu et al., 2008). Additionally, small quantities of fat are generally required for reconstructions in the head and neck, as compared to other regions, such as the breast, thus manual pressure aspiration harvesting is efficient and widely used.

Many types of cannulas have been imagined for fat harvesting, considering the cannula diameter, the number of holes and their sizes and the preference for using any of them is different among surgeons. Still, the Coleman's technique serves as a reference for all other protocols since it has shown favorable outcomes in terms of fat viability and it is considered the most routinely used method for harvesting the adipose tissue. It consists of injecting the tumescence solution (a mixture of 0.5% lidocaine and epinephrine 1:200,000) at the level of the harvesting sites, followed by aspirating the fat using a 10 ml syringe connected to a 3 mm blunt cannula with two holes under mild manual negative pressure (Coleman, 1997; Kaufman et al., 2007).

Following harvesting, the processing of the adipose tissue is performed, involving techniques like sedimentation, filtering, washing or centrifugation with the purpose of separating only the viable components of the lipoaspirate. Many of the developed processing methods render favorable outcomes, which is why there is no current consensus regarding the most effective method (Galiè et al., 2008).

The method described by Coleman involves centrifugation at 3000 rpm for 3 minutes, resulting in three separate layers: a top oil layer as the result of burst adipose cells, a middle high-density layer containing usable fat tissue and where the stem cells are also found, and a bottom liquid layer of blood mixed with tumescence solution (Kaufman et al., 2007; Pu et al., 2008; De Francesco et al., 2017). Although this processing protocol rendered optimal clinical outcomes, it has been proposed that lower spinning forces of approximately 1300 rpm for 5 minutes may further enhance the viability of the adipose tissue (Ferraro et al., 2011).

Additional methods for increasing the benefits of fat grafting are the addition of bio-enhancers, the use of synthetic three-dimensional scaffolds and cell-assisted lipotransfer which involves grafting using fat enriched with adipose-derived stem cells obtained after enzymatic digestion or cell culture (Brett et al., 2017; Matsumoto et al., 2006).

2.1.4 Techniques of fat engrafting

After harvesting and processing, the adipocytes can be injected anywhere at the level of the maxillofacial territory, by using cannulas of different shapes and sizes, for filling defects of various sizes and origins (Khan, Keyhan, 2018; Obagi, Willis, 2018).

To conserve more adipocytes, Coleman emphasizes the importance of practicing the least traumatic technique for harvesting and injecting, insisting that a minimal amount of fat should be transferred into several tissue tunnels, in layers, in order to maximize the contact surface with the surrounding tissue and enhance adipocyte neovascularization (Coleman, 1995). Injecting thin layers with the help of cannulas allows the formation of a tridimensional structure in which the adipocytes are easily vascularized, so that their viability and functional character is preserved (Coleman, 2001; Mazzola, Mazzola, 2015; Bagheri et al., 2018).

Many authors enthusiastically recommend using autologous fat transplantation for the reconstruction of facial deformities, reporting high rates of survival of the autologous fat grafts and few complications (Mazzola, Mazzola, 2015). Some of the comments offered by those with experience in the use of these tissue grafts relates to: 1) the need for injecting small or moderate amounts of fat in each treatment, 2) the best results are seen when fatty grafts are injected subfascial or intramuscular, 3) fat injections should be made deep in several places in the form of fine droplets or small rolls, 4) massage the areas injected with fat to ensure the fat penetration.

Considering the technique preferred by different surgeons, the injection can be performed in a single plane or in a tridimensional manner. The essential aspect in all cases in that the graft must be deposited in very thin layers that can be easily revascularized (Gause et al., 2014; Bagheri et al, 2018). This process is also facilitated by the significant amount of stem cells that are found in the grafted adipose tissue. In this way, tissue regeneration is obtained simultaneously with restoring the deficient volume, an even more important aspect when correcting postoperative defects.

2.1.5 Applications of autologous fat grafting in oral and maxillofacial surgery

Autologous fat grafting is a technique used in reconstructive surgery to reshape the soft tissues, as recommended by a lot of advantages: it can be performed under local anesthesia, it requires short execution time, the availability of the reconstruction material is unlimited, there are no additional scars, no morbidity in the donor site, the procedure can be repeated to achieve the desired effect with minimum discomfort to the patient and it has good aesthetic and functional results that are stable over time. In addition, the multipotent mesenchymal cells capital associated to the fat cells significantly improve the texture and nourishment of all the tissues in the area where fat grafting is performed, tissues that are often modified by tumor excision surgery or by additional radiotherapy and chemotherapy (Clauser et al., 2018)

Though used in plastic surgery for a long time, the fat graft gained great popularity in the last 20 years. This is largely due to the qualities of the ideal filler of this material: natural, stable, uncomplicated, autologous, thus entirely biocompatible, available in large quantities for most patients and easily integrated in the receiving tissue. Therefore, it is not surprising that structural fat grafting gradually developed as a natural option for the reconstructive surgery of the face (Krastev et al., 2018). The indications are numerous: tissue atrophy, posttraumatic defects, post tumoral resection defects, complex congenital craniofacial deformities, burns, post-irradiation tissue changes and progressive hemifacial atrophy (Romberg syndrome, scleroderma) (Diepenbrock, Green, 2018; Denadai et al., 2019).

2.2. AUTOLOGOUS FAT GRAFTING FOR THE REHABILITATION OF THE PERIOCULAR REGION

Soft tissue scarring and malposition in the periocular area can result in unpleasant symptoms, but also functional impairment that can even progress to complications endangering vision. The thin and anatomically complex local soft tissues are difficult to reconstruct surgically due to the morbidity associated with postoperative scars in the periorbital region. Minimally invasive techniques with added regenerative advantages, like structural fat grafting, greatly benefit the rehabilitation of this frail and anatomically dense area of the face (Coleman et al., 2018; Romeo, 2019).

Considering the potential for volume optimization, as well as the qualitative improvement of the local tissues, the utility of structural fat grafting in the reconstruction of the delicate periocular region is the subject of continuous research (Çetinkaya, Devoto, 2013; Le et al., 2014; Boureaux et al., 2016; Lupo et al., 2016; Pelle-Ceravolo, Angelini, 2019), in an attempt to improve results and the quality of life of patients.

The constant interest for studies regarding structural fat grafting, and the good reported outcomes of this procedure in the area of head and neck reconstruction, determined us to include autologous fat grafting as a main research interest for our group, identifying several specific topics for the doctoral studies. The results we obtained so far were analyzed in a PhD thesis (Drochioi, 2017) and published in an original manuscript:

- ✓ Drochioi C, Costan VV*, Zaharia M, Boisteanu O, Sandu IG, Earar K, Popescu E. FT-IR characterization of some biological materials used in reconstructive surgery. Rev Chim 2015; 66(9):1302-1305.

The purpose of the study was to assess the outcomes of autologous fat grafting in the functional and aesthetic rehabilitation of the periorbital area, in order to improve the future management of patients with periorbital defects and contribute to the existing literature.

2.2.1. Materials and method

We performed a retrospective study by reviewing the medical charts of patients who underwent autologous fat grafting in between 2009 and 2019, for the correction of congenital or acquired defects associated with periorbital volume deficit and eyelid malposition. We present the fat harvesting protocol and the injection technique. In our study we included only patients with a minimum of six months and up to ten years of follow-up. The etiology of the defect, the main complaints, as well as the postoperative outcomes were all documented.

2.2.2. Results

- **Clinical characteristics**

A total of 31 patients were included in the study, of which 10 women and 21 men, aged between 17 and 69 years. The etiology of the defects was posttraumatic in 10 patients, congenital anomalies in three cases, and tumoral resections in the other 18 cases. From the postoperative defect group, facial nerve paralysis involving the zygomatic branch was present in 14 patients. In 17 patients, other reconstructive procedures were performed prior to lipofilling for the improvement of facial asymmetry and eyelid malposition, with insufficient results. Minimally invasive static reanimation procedures consisting of suture suspension were previously performed for 11 of the facial paralysis patients. In three of those patients barbed threads were used for tissue suspension.

The main objective findings were the presence of lagophthalmos (14), inferior eyelid ectropion (9) and volume loss of the periorbital tissues (23). In 11 patients a retractile scar in the periorbital region was present. Five patients complained of ocular pain, two of epiphora, 18 described xerophthalmia, and seven associated blurred vision. Nine patients had previous mechanical and infectious ocular complications treated medically by the ophthalmologist.

Preoperative planning involved the assessment of the amount and location of the volume deficit. The necessary amount of fat to be harvested was estimated and one or several procedures spaced 6 months were planned where indicated. The patients were evaluated by clinical and photographic analysis.

- **Therapeutic approach**

Over the course of the 11 years included in this retrospective study, two main techniques of fat harvesting and processing were used, regarding the instruments used and the centrifugation protocol. The change in protocol was related to updating the technique used to the more recent recommendations in the literature. The amount of fat to be harvested was according to the established deficit and limited by the amount available at the donor site. If necessary, a second donor site was used.

The intumescence solution was prepared using 500 ml saline, 20 ml of 1 % lidocaine and 5,1 ml of 4% articaine with 1:100.000 adrenaline. Prior to harvesting, it was injected via a 50 ml syringe into the fat tissue in the donor area using an injection cannula. The harvesting cannulas were inserted through very small holes made in the natural folds using the tip of a number 11 blade (Fig. 2.2.1.).

In 14 patients, 3 mm cannulas were used for hand pressure harvesting, attached to a 50 ml syringe, followed by the centrifugation of the fat at 3000 rpm for 5 minutes. In 17 cases the fat was harvested using low pressure hand aspiration via a 10 ml syringe attached to cannulas with holes of 1 mm. Consequently, the harvested fat was centrifuged at 1500 rpm for 10 minutes (Fig. 2.2.2.).

After centrifugation, three layers resulted, containing oil, adipocytes and blood (Fig. 2.2.3.). The oil and the blood layers (the top and the bottom layer) were discarded. The middle layer containing the fat was then transferred to the injecting syringe attached to an injection cannula. The 18 G injection cannula was inserted through skin punctures at the recipient site, performed using a 17 G needle (Fig. 2.2.4.). The harvested fat was then injected at the level of the defect into thin layers, arranged in several planes, in a fan-like manner.

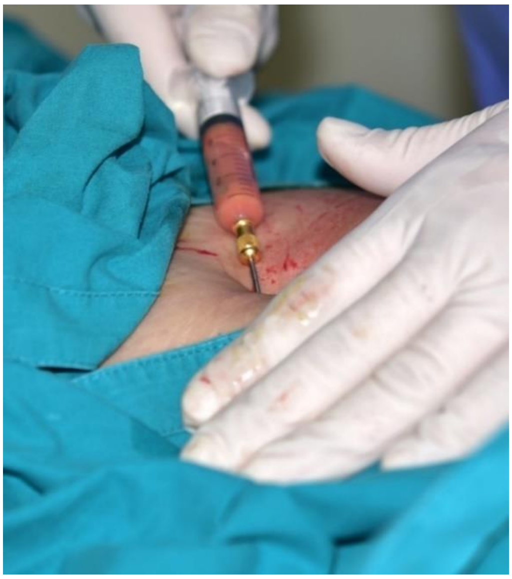

Fig. 2.2.1. Fat harvesting from the periumbilical area through umbilical scar using a 10 ml syringe

Fig. 2.2.2. Fat processing by centrifugation at 1500 rpm for 10 minutes

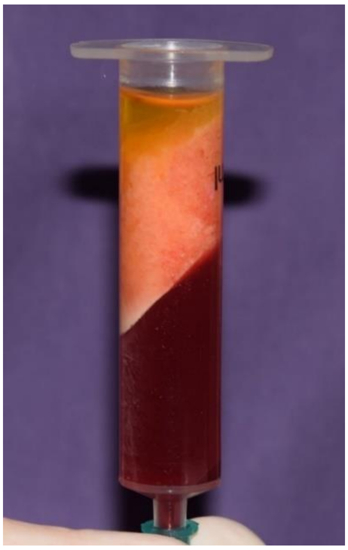

Fig. 2.2.3. The aspect of the harvested fat after centrifuging, resulting in three layers

Fig. 2.2.4. The injection cannula was inserted through skin punctures

The procedure was performed under local anesthesia with intravenous sedation in 23 cases and under general anesthesia in eight cases. The harvesting site was the abdominal region in all cases. Additional harvesting from the thighs and flanks was performed in three cases because the periumbilical area alone failed to provide the entire necessary volume of fat.

The injected quantities varied between 10 and 35 ml, with an average volume of 22,5 ml. Most patients (26) had autologous fat grafting involving several areas of the hemiface. The fat was injected unilaterally, at the level of minimum one area of the face: the inferior eyelid (17), external canthus (9), genian region (15), zygomatic region (12), temporal region (8), facial scar (21).

The postoperative outcomes were assessed clinically by follow-ups at 7 days, one month, 3 months and six months postoperative, and photographically documented.

- **Surgical outcomes**

Postoperative, all patients experienced small intensity pain in the injected area, accompanied by a discrete edema. Bruising occurred in 11 patients. There were no infectious complications. No significant amount of graft loss was noted at one month and six-month follow-up.

A successful rehabilitation of the periocular region was achieved in all cases. Facial asymmetry improved, with good restoration of the periorbital volume and of the volume of the surrounding supporting regions: the zygomatic, genian and temporal regions, when involved. An improved palpebral competence was achieved in all patients presenting with lagophthalmos, with a decrease of complaints and complications related to corneal exposure. Additional methods for further improvement were necessary in three facial paralysis patients for the improvement of symptoms related to lagophthalmos. The position of the lower eyelid in relation to the globe improved in all ectropion cases. Facial scar texture, elasticity and overall appearance were ameliorated, with a decrease in the subjective complaints of the patients.

The good aesthetic and functional outcomes were reached with one injection session in 20 patients. Eight patients needed two sessions for achieving the desired result, and in three patients, three sessions were performed, spaced minimum six months apart. Multiple sessions were initially planned due to the important volume deficit in nine cases. In two patients the amount of fat necessary was underestimated initially. In three patients the repetition of autologous fat grafting was due to small irregularities noticed postoperative in the inferior palpebral areas. No relevant correlation could be demonstrated between the type of fat harvesting and processing and the achieved outcomes.

The results obtained after each session remained stable after six months, except two cases in which an increase in the volume of the injected fat resulted in slight excess, as a consequence of the patient gaining weight in the months following autologous fat grafting. The excess was not associated with functional disturbances or important changes in the appearance and thus did not necessitate any corrections.

The outcomes of autologous fat grafting are presented through two examples of cases (Fig. 2.2.4.- 2.2.11.).

Fig 2.2.4. Example 1: Patient with left facial paralysis after surgery for a malignant parotid tumor. The image shows the paralytic left inferior eyelid ectropion with soft tissues ptosis, periorbital volume deficit and facial asymmetry (Drochioi, 2017)

Fig 2.2.5. Example 1: Clinical aspect of the patient during eye closure showing left lagophthalmos (Drochioi, 2017)

Fig 2.2.6. Example 1: Aspect of the patient after autologous fat grafting in the inferior eyelid, superior genian and zygomatic regions, showing decreased eversion of the inferior eyelid due to the improved support offered by the local volume increase (Drochioi, 2017)

Fig 2.2.7. Example 1: Clinical view of the patient during eye closure, showing good palpebral closure with disappearance of left lagophthalmos due to the increased volume of the inferior eyelid (Drochioi, 2017)

Fig 2.2.8. Example 2: The deepening of the left orbital region after an untreated naso-orbito-ethmoidal fracture – frontal view (Drochioi, 2017)

Fig 2.2.9. Example 2: The deepening of the left orbital region after an untreated naso-orbito-ethmoidal fracture (Drochioi, 2017)

Fig 2.2.10. Example 2: Restoring symmetry of the orbital region after autologous fat grafting- frontal view (Drochioi, 2017)

Fig 2.2.11. Example 2: Restoring of the orbital region symmetry after autologous fat grafting (Drochioi, 2017)

2.2.3. Discussions

Depending on the etiology, eyelid malposition can be addressed by performing various repositioning procedures such as lateral canthopexy, lateral tarsorrhaphy, suspension sutures, fascial slings, skin or cartilage graft insertion, or the use of local flaps (Hahn, Desai, 2017; Chambers, Moe, 2017; Karadeniz Uğurlu, Karakaş, 2017). The downside of all surgical approaches in the periorbital region is the secondary surgical scarring and contracture in the incision and dissection area. The need for maintaining the characteristics of the periocular skin regarding thickness, texture, laxity and mobility, or the wish to restore these normal features, recommend autologous fat grafting as a procedure of many benefits for this particularly delicate anatomical region. The minimally invasive technique of structural fat grafting avoids the disadvantages associated with open surgical procedures. The repositioning of the eyelid is rendered by adding volume in target areas, while the adipose-derived stem cells contained in the lipograft ensure an improvement in the quality of the local tissues.

Although, frequently, several procedures are necessary for achieving good functional and aesthetic outcomes in the rehabilitation of the periocular region, some authors reported good results in selected cases, by the single use of autologous fat grafting (Lupo et al., 2016). In our experience, fat grafting proved to be a valuable reconstructive tool both to complete the results obtained by previous surgeries, but also as a standalone treatment, when the indication was accurate.

In paralytic lagophthalmos we obtained good results with minimal patient discomfort by the association of two minimally invasive procedures performed separately, for tissue repositioning and filling: incisionless barbed suture suspension and subsequent autologous fat transfer. The advantages are the possibility to perform the procedures under local anesthesia, minimal to no scarring, but also that they can be repeated for reaching and maintaining the desired results. The injected fat into the inferior eyelid and genian regions is designed to support the lower eyelid, so that the decreased tone of the orbicularis oculi muscle can be compensated. This effect contributes to a better eyelid occlusion. Under-correction is generally easier to treat than overcorrection. Additional fat may be grafted in a separate session to complete the correction. Removing excess graft is more difficult as the host tissue blends into the graft.

The best technique of fat harvesting is a subject for debate between different authors and further standardization is needed (Fontes et al., 2018). Still, the general results obtained by structural fat grafting are mainly positive as presented by the majority of studies (Coleman et al., 2018; Riesco et al., 2018; Romeo, 2019), regardless of minor differences in harvesting area, intumescence, harvesting equipment and technique, as well as processing and injection technique (Gause et al., 2014; Frame, 2018; Bagheri et al. 2018). The good outcomes were also shown in our study regarding both function and appearance. Our preference for harvesting fat is using a technique and instruments that reduce the trauma on the adipose tissue to be aspirated. We use low pressure hand aspiration using a syringe and multiperforated cannulas. The tissue is previously injected with a high volume of intumescence solution. Using cannulas with multiple small holes of 1 mm for fat aspiration, also helps decrease the pressure while injecting the fat.

The injecting technique is different among various surgeons, but it is of outmost importance for increasing the chances of graft survival, but most importantly for achieving the desired results. Most authors agree that the thinner the layers deposited in the tissues, the greater the chance for fat graft survival and integration (Frame, 2018; Bagheri et al. 2018; Clauser et al., 2019). In addition to this, we consider that the depth of injection is another important issue in obtaining the desired volume change, considering the extensibility of the receiving area, the distribution and migration of the injected fat. This is particularly important in the lateral canthus area, where a more pronounced lift can be achieved by a deep juxta-periosteal injection, into firmer tissues. In the same manner, a very superficial injection can result in irregularities, particularly in the thin soft tissues of the periocular area (Çetinkaya, Devoto, 2013). Irregularities were observed in two of our patients in which a reinjection was necessary for uniformization of the appearance. The use of microcannulas for injection, zigzag deposition and massaging the region after the deposition of the fat can help reducing the risk of irregular surface. This was also emphasized by other authors (Obagi, Willis, 2018). When a greater volume within one session is desired, the thin layers of fat can be deposited at different tissue depths, for ensuring maximum chances for vascularization and survival of the grafted adipose tissue. A layered linear deposition of the fat starting deep from the periosteum and gradually arriving towards the superficial subcutaneous plane is also recommended by Clauser (Clauser et al., 2018).

The cannula injection itself has been advocated to improve symptoms related to the presence of scars. The dissection performed by cannula insertion determines the release of scar tissue and is associated with a decrease in local pain (Riyat et al., 2017). By creating a tunnel, it also decreases the pressure necessary for fat injection. Autologous fat grafting itself further contributes to the analgesic effect by providing adipose-derived stem cells, stimulation of angiogenesis and an anti-inflammatory effect. Similar to the results of other studies (Caviggioli et al., 2008; Lupo et al., 2016; Riyat et al., 2017), we also noticed an improved appearance of the facial scars and cicatricial ectropion following lipofilling, as well as a decrease in the subjective complaints of the patients.

Sufficient volumes of fat can be injected in this layered fashion, but in certain cases where an important volume increase is necessary, it might be safer to plan for multiple injection sessions. Additionally, multiple sessions are necessary when there is a limited amount of fat tissue available at the donor site. The interval between two injections of fat can vary from 3 months to 12 months, by different authors (Lupo et al., 2016; Boureaux et al., 2016; Clauser et al., 2018). Some authors performed the reinjection for cicatricial ectropion three months after the initial procedure with positive outcomes (Lupo et al., 2016). We prefer to space the procedures minimum six months apart for a more accurate definition of the postoperative tissue changes in the injection area.

In our case series we injected between 10 and 35 ml of fat, with an average volume of 22,5 ml, distributed most often in several facial subunits, according to the desired outcome. Other authors report an average of 25,7 ml per side in the cheek and midface regions (Shue et al., 2017). Coleman (Coleman, 2006) reported injecting an average of 26,5 ml in the temple, brow and superior eyelid regions, while Xie (Xie et al., 2010) reports volumes as low as 1,2 ml average in the periocular area. Le (Le et al., 2014) injects an average of 6 ml of fat in the inferior eyelid, tear trough and malar region. The volumes vary greatly considering the regions involved, the quality of the tissues, the spatial configuration of the defect, the technique preferred by the surgeon, the number of sessions scheduled, but mainly considering the injection purpose- aesthetic, reconstructive or regenerative.

Using a cannula for fat injection can help minimize the risk of embolic complications, such as occlusion of the central retinal artery or cerebral infarction (Boureaux et al., 2016; Kim et al., 2017). This is outlined by previous studies regarding structural fat grafting injection technique (Le et al., 2014; Simonacci et al., 2017), and it is one of the main reasons we prefer using a blunt tip microcannula, along with a slow retrograde injection technique under minimal pressure. Good knowledge of anatomy, particularly the location and course of the main regional blood vessels is of outmost importance in preventing such complications, alongside the technique. Regions associated with a higher risk of fat embolism are the glabella and rarely the superior eyelid (Boureaux et al., 2016; Simonacci et al., 2017). Performing the procedure under local anesthesia with sedation helps in the early recognition of the arterial occlusion since it is associated with severe pain.

Like stated by other authors we mainly encountered minor complications (Krastev et al., 2018), involving edema and bruising. Edema was usually evident for one to two weeks after the procedure. Bleeding complications usually were limited to transient mild ecchymosis with rapid resolution. The absence of postoperative hematomas in our study is due to our preference for blunt cannula injection, instead of using sharp instruments more often associated with such complications. Damage to underlying periocular structures is also avoided by using blunt devices for infiltration. Although infectious complications may exceptionally occur in the donor or recipient regions (Krastev et al., 2018), we did not encounter any in our case series. Another possible occurrence is the presence of minor irregularities in the reconstructed region or even excessive corrections, that may need secondary reshaping procedures. Tissue scarring in the donor site is a potential concern, resulting from overly aggressive harvesting performed in a small area.

The desired contour and volume obtained postoperative were evaluated after the resolution of edema, one week and one month after surgery. The results were maintained beyond six months, but in two patients, a hypertrophy of the injected fat occurred. This was associated to the patient gaining weight mainly in the area of fat harvesting- the abdominal region. Other authors noted this outcome that, in some studies, necessitated difficult correction procedures (Coleman et al., 2018; Krastev et al., 2018; Pelle-Ceravolo, Angelini, 2019).

Concluding remarks

Our study demonstrated positive outcomes regarding the restoration of facial symmetry, improving eyelid malposition and the appearance of periorbital scars, as well as decreasing the patients' subjective complaints. This translated into both esthetic and functional improvements with minimal complications in the grafted region.

We consider that the injection technique regarding the amount and location of deposition of the grafted fat contributed most in the good results obtained in our study. The three-dimensional distribution of the thin fat in layers in the receiving area, adapted according to the preoperative defect evaluation, allowed for individualized treatment and optimal results and fat integration.

Both the volumizing and the regeneration aspects of structural fat grafting are important in recommending this technique for the rehabilitation of anatomical areas that are difficult to reconstruct surgically, such as the periocular area. Used alone, or in association to other reconstructive techniques, this procedure can result in qualitative and quantitative improvements in the structure of the periorbital tissues.

2.3. AUTOLOGOUS FAT GRAFTING FOR THE FUNCTIONAL REHABILITATION OF THE PERIORAL AND ORAL REGIONS

The integrity of the perioral and oral regions is essential in ensuring normal function exertion regarding mastication, deglutition and phonation. Local scars and changes in the quantity and quality of the local tissues have a negative impact, determining functional disturbances of various degrees. Even minor changes involving these anatomically significant areas may cause major complaints and decrease the quality of life of the patients since they interfere with vital functions, but also affect the social life. Repeated corrective open surgery aimed at improving local scars and anatomic contours may sometimes worsen the outcomes due to added scar tissue. Autologous fat grafting has multiple advantages to open surgery in the rehabilitation of such defects, since it allows the avoidance of supplementary scars, while also filling and improving the quality of the local soft tissues due to the presence of mesenchymal stem cells in the grafted adipose tissue (Clauser et al., 2018; Krastev et al., 2018; Jackson et al., 2020).

The structure and functions of adipose tissue have been the focus of numerous studies in an attempt to better characterize it, define the indications of autologous fat grafting and expand its clinical use for the benefit of patients with different complaints. It contains a large amount of fat cells and mesenchymal stem cells that can differentiate into several connective tissue-type cell lines. Therefore, structural fat grafting allows not only a volume restoration, but also the improvement of the tissue characteristics, useful in areas of atrophied scar tissue (resulting from trauma, or surgery with radiotherapy and/ or chemotherapy) (Coleman et al. 2018; Clauser et al., 2018; Krastev et al., 2018). As a result, the texture and the nutrition of the skin (and other tissue layers where lipofilling was performed) will significantly improve. The injected mesenchymal stem cells, on the one hand, turn into young fibroblasts and, on the other hand, stimulate neovascularization with beneficial effects on the scar tissue, including an increase in local tissue hydration (Coleman et al. 2018; Clauser et al., 2018).

To enrich the existing knowledge regarding the properties of adipose tissue that contribute to the favorable functional outcomes achieved by autologous fat grafting in reconstructive surgery, we published the following manuscript:

- ✓ Timofte D, Mocanu V, Eloae FZ, Hristov I, Cretu IS, Aursulesei V, Balan GG, Ciuntu BM, Oboroceanu T, Tiron A, Costan VV*, Butcovan D. Immunohistochemical expression of growth hormone secretagogue receptor (GSH-R) of adipose tissue macrophages in obese bariatric patients. Rev Chim 2019; 70(9):3428-3430.

The purpose of this study was to outline the benefits of autologous fat grafting for the functional restoration of various defects in the perioral and oral regions, in order to refine the technique and expand the indications of the procedure in our future practice.

2.3.1. Materials and method

We reviewed the medical records of patients that underwent autologous fat grafting for the functional rehabilitation of the perioral and oral regions over the course of 11 years, from 2009 to 2019. Only patients with at least one functional complaint upon presentation were included in the study. Patients with solely aesthetic disturbances were excluded, as well as patients with less than 6 months of follow-up. We analyzed the general information, the diagnosis, the primary complaints, the findings upon clinical examination, the technique of autologous fat grafting and the outcomes.

2.3.2. Results

- **Clinical characteristics**

A total of 28 patients fitted the inclusion criteria, 17 men and 11 women, aged between 17 and 61 years old. There were six patients with sequelae following cleft lip surgery, seven cases of sequelae following perioral trauma, seven patients with an operated oral cancer and tongue reconstruction, and eight patients with operated lip and skin malignancies in the perioral regions. Clinical examination outlined the presence of retractile scars (17), contour deficiencies (21) and volume deficiencies of various degrees (28). Nine patients had incomplete lip closure and six patients had limited mouth opening. Phonation disturbances were encountered in 16 patients, while 18 reported mastication difficulties and 9 had difficulties in deglutition.

- **Therapeutic approach**

Autologous fat grafting was performed under local anesthesia with monitoring and intravenous sedation in 27 patients and under general anesthesia in one case. The fat was harvested from the abdomen in all patients, after the infiltration of the tumescence solution. In two patients in which a greater quantity was needed, the thighs were used as additional harvesting sites.

Harvesting was performed using larger bore cannulas of 3 mm in 12 patients and then centrifuged for 5 min at 3000 rpm. In the other 16 cases, the fat was harvested using small bore cannulas of 1 mm with subsequent centrifugation for 10 minutes at 1500 rpm. The resulting centrifuged fat was then injected using an injection cannula in a retrograde layered manner, at the desired level in the oral and perioral regions. The tongue and tongue base were augmented in seven patients, the superior lip was injected in 12 cases, the inferior lip and labio-mental region in 14 patients, the genian region and oral commissure region in 8 cases. In 11 patients, the recipient sites were multiple. The quantity injected varied between 10 and 35 ml of centrifuged fat.

Patients were evaluated by clinical examination at one week, one month, three months and six months after surgery. The outcomes were documented by clinical photography and analyzed.

- **Surgical outcomes**

Pain in the harvesting and in the injection region and discrete local edema were the most common occurrences after the procedure. More noticeable bruising was seen in 7 patients. We did not encounter any significant complications during harvesting or grafting.

The volume increase in the grafted areas was evident immediately after the procedure in all patients and maintained at three- and six-months post-procedure in 24 cases. In four patients there was a slight decrease in the volume of the injected area after 3 months and a new grafting session was scheduled. Several injection sessions were needed for 12 patients to reach the desired result. In 3 patients, there was a volume increase after 12 months due to the patient gaining weight. Irregularities in the grafted area were encountered in 2 cases at 6 months post-injection.

Lip closure improvement as well as a functional improvement regarding mastication, deglutition and phonation were noticed immediately after the procedure in the patients with these initial complaints.

A softened aspect of the local scars and improved tissue mobility was evident in all patients at six months after fat grafting. A functional improvement regarding mouth opening and tissue mobility was seen in all patients with such complaints six months after the procedure.

The positive outcomes are outlined by two examples of cases (Fig. 2.3.1-2.3.8).

Fig. 2.3.1. Example 1: Patient with sequelae following cleft lip surgery. Image shows incomplete lip closure at rest due to deficient soft tissue volume, contour deformity and retractile scars in the superior lip region (Drochioi, 2017)

Fig. 2.3.2. Example 1: Patient with sequelae after cleft lip surgery. Clinical aspect during mouth opening outlining the contour deformity and the retractile scar tissue in the superior lip region (Drochioi, 2017)

Fig. 2.3.3. Example 1: Clinical aspect of the patient following autologous fat grafting in the superior lip region, demonstrating the augmented superior lip volume, symmetric contour, softened scars and proper lip closure at rest (Drochioi, 2017)

Fig. 2.3.4. Example 1: Clinical aspect of the patient following autologous fat grafting in the superior lip region. Inferior view demonstrating the superior lip symmetry with restored volume and contour, scar release and adequate oral competence (Drochioi, 2017)

Fig. 2.3.5. Example 2: Frontal view of a patient three years after the removal of an extended carcinoma of the lower lip region. The defect was reconstructed using a radial free flap. The red of the lip was restored using a tongue flap. The image shows the presence of retractile depressed scars and constricted aspect of the inferior lip, causing decreased mobility of the lip and difficulties in maintaining good oral competence during mastication and phonation

Fig. 2.3.6. Example 2: Left profile view of the patient three years after the removal of the extended inferior lip region carcinoma, showing the absence of volume in the inferior lip and lack of chin projection

Fig. 2.3.7. Example 2: Frontal view of the patient one year after autologous fat grafting in the mental and inferior lip region showing improved aspect of the postoperative scars and increased volume and length of the inferior lip with improved oral competence resulting in favorable functional outcome

Fig. 2.3.8. Example 2: Left profile view of the patient one year after autologous fat grafting showing the increased volume and projection of the inferior lip and mental regions

2.3.3. Discussions

Perioral and oral changes in the appearance and function of tissues are encountered in various pathologies, most often in relation to previous surgery or trauma. Restoring the anatomical features characteristic to these areas is essential for a pleasant appearance, but also for the proper functioning of the mobile tissues with this location, that contribute in speech, mastication and deglutition. Regardless of the etiology of the defect, autologous fat grafting ensures a minimally invasive means of local rehabilitation (Clauser et al., 2019).

In our study, there were six cases of patients with secondary deformities following cleft lip surgery. Ensuring an optimal quality of life for these patients involves an aesthetic and functional rehabilitation of the perioral area. Deficient volume and asymmetric contour in the superior lip are common findings after cleft lip repair. In addition to the poorly developed soft tissues, the postoperative scars in the upper lip region often cause traction on the nostril and vermillion, further accentuating the asymmetry, but also often causing incomplete lip closure with consequences on mastication and phonation (Jackson et al., 2020). Many authors underline the utility of autologous fat grafting in volumizing the superior lip region, improving the aspect and feel of preexisting scars and correcting the position of the nostril, with an overall improvement of facial symmetry (Clauser et al., 2011; Koonce et al., 2018; Jones et al., 2017).

The integrity of the soft tissues forming the boundaries of the oral cavity must be ensured after the resection of carcinomas with this location. However, the quantity of the local tissues available for reconstruction is limited and may restrict the normal movement of local tissues, even when an additional regional or distant flap is used for reconstruction. Since primary closure of the defect is desired in order to allow alimentation, this is often performed under tension, or lacking sufficient volume, with consequences on the overall functioning of the area. We achieved favorable outcomes in volumizing deficient areas and increasing tissue quality and mobility by performing autologous fat grafting in the perioral region previously reconstructed with flaps. This is also reported by other studies attempting functional restoration by fat grafting in addition to local open reconstructive procedures (Vitagliano et al., 2016).

Even more than the cutaneous perioral region, adequate tongue reconstruction following oral cancer resection is essential for resuming proper mastication and deglutition. The greater the defect, the more challenging the reconstruction in ensuring the characteristics necessary for optimal function. In extensive resections, it is advisable to ensure posterior tongue bulk for the posterior propulsion of food during deglutition. In free flap reconstruction, ensuring proper volume may be difficult, since some reconstructive options offer little volume, like the radial free flap, while others render initial excessive bulk, like the latissimus dorsi free flap. In addition, the muscular component of flaps atrophies in time with a consecutive decrease in volume. In our experience, autologous fat grafting of the reconstructed tongue and tongue base can ensure supplementary volume and improve deglutition. Multiple injection sessions may be necessary to achieve the desired volume, since the amount of fat that can be injected in one session is generally limited in order to ensure maximum taking of the graft. Longo et al. also underlined the benefits of using autologous fat grafting for increasing the volume and refining results in reconstructive procedures using the radial free flap (Longo et al., 2019). Navach et al. performed autologous fat grafting in the tongue base for improving post-irradiation dysphagia with good outcomes (Navach et al., 2011).

We saw improvements in the aspect and feel of the perioral scars in addition to the volumetric growth in all the patients included in the study, which translated into improved functional outcomes. The good results were attributed mainly to less scar traction on the local tissues which improved mobility and opening during mastication and phonation. Additionally, the added volume to the deficient regions contributed to achieving proper lip closure. The outcomes were favorable regardless of the etiology of the defects. Similar positive results are reported by authors in studies regarding the reconstruction of perioral defects of various etiologies, including cleft lip deformities, the removal of lip carcinomas (Sykes et al., 2010; Clauser et al., 2011; Vitagliano et al., 2016; Koonce et al., 2018).

The most obvious and constant improvement, encountered in all our patients, was the softening of the local scar tissue with improved overall aspect. This in turn rendered increased tissue mobility and contributed to the functional restoration. Other studies have also shown positive changes in tissue quality following autologous fat grafting in the perioral region, with resulting softening of the tissues, increased oral perimeter and increased amplitude of mouth opening (Vitagliano et al., 2016; Del Papa et al., 2015). Furthermore, fibrous perioral changes associated with systemic conditions like scleroderma have also been improved by autologous fat grafting, to such an extent that repeated injection sessions are considered as local treatment recommendation (Del Papa et al., 2015).

Another important fact recommending this procedure for patients with retractile perioral scars is that studies have shown an improvement of tissue quality even when the intended volume was not achieved, thus ensuring that even in the event of partial or complete graft resorption, the benefits rendered by the mesenchymal stem cells contained in the grafted fat are still present and a degree of functional improvement will nevertheless be obtained (Del Papa et al., 2015). This was also true for the cases in our study, since the favorable change in soft tissue quality was encountered in all patients and was constant in time, regardless of the obtained volume increase that slightly fluctuated within six months for a small number of patients.

Concluding remarks

In our experience, autologous fat grafting is suitable for the functional restoration of the perioral and oral areas since it allows a minimally invasive, scar-less approach to improve both tissue quality, mobility, and volume. Contour deficiencies and retractile scars of various etiologies can be improved using this technique. Repeated sessions allow reaching the desired outcome in cases requiring greater volume augmentation or refining previous results.

2.4. RECONSTRUCTIVE SURGERY USING AUTOLOGOUS FAT GRAFTING IN ONCOLOGIC PATIENTS

Increasing the life quality of oncologic patients is a current focus of many research studies since the survival of the patients is greatly increased as a consequence of the continuous treatment advances. Both tumor resection surgery and radiotherapy are the culprits for the functional and aesthetic sequelae encountered in patients with treated head and neck cancers. Autologous fat grafting can greatly benefit various types of defects following malignant tumor resection and reconstruction, by improving the volume, contour and quality of the tissues without additional scars (Karmali et al., 2018; Hammond et al., 2019).

In the interest of expanding knowledge regarding the benefits of autologous fat grafting for improving reconstructive outcomes in oncologic cases, we published the following:

- ✓ Costan VV, Trandafir D, Popescu E, Drochioi CI. Autologous fat transfer to reconstruct facial defects after parotidectomy. In: Costan VV (ed) Management of Extended Parotid Tumors. Springer, 2016.
- ✓ Drochioi CI, Sulea D, Timofte D, Mocanu V, Popescu E, Costan VV. Autologous Fat grafting for craniofacial reconstruction in oncologic patients. Medicina (Kaunas, Lithuania) 2019; 55(10). pii: E655.

The purpose of this study was to evaluate the outcomes of autologous fat grafting in improving the functional and aesthetic outcomes in patients with operated head and neck cancers, in order to expand the indications of this technique in oncologic cases and contribute to the scarce existing literature on the subject.

2.4.1. Materials and method

We reviewed the medical files of patients with previously operated oral and maxillofacial cancers that underwent autologous fat grafting in the head and neck area, over the course of 11 years, from 2009 to 2019. Only patients with minimum six months of follow-up were included in the study. The general patient information, the initial diagnosis, main complaints, the technique and site of injection, as well as the post-injection outcomes were all documented.

2.4.2. Results

- **Clinical characteristics**

A total of 32 patients were included in the study, aged between 47 and 74 years old. There were 18 men and 14 women. The initial operated malignant condition was represented by lip and oral cancers (11), skin carcinomas (6) and parotid gland malignancies (15). From the included patients (23) had a history of postoperative radiotherapy in the head and neck regions. The patients presented for one or several of the following complaints: facial asymmetry (25), retractile scars (16), limited movement (14), dysphagia (7), local pain (29). The time interval between tumor removal surgery and autologous fat grafting was minimum one year and maximum 4 years. All patients were initially assessed by clinical examination and imaging studies to exclude locoregional or distant tumor recurrence.

- **Therapeutic approach**

The procedure was performed under local anesthesia in 30 patients and general anesthesia in two cases. The harvesting sites for the adipose tissue were the abdomen in 29 cases, and the abdomen and thighs in three cases. For the harvesting and processing of the fat we used two main techniques. In 15 cases the fat was harvested using a 50 ml syringe with a 3 mm cannula and then centrifuged at 3000 rpm for 5 minutes. For the other 17 patients, a 10 ml syringe was used connected to a 1 mm cannula, followed by centrifugation at 1500 rpm for 10 minutes.

The fat was then injected at the level of the parotid region (19), cervical region (13), submandibular region (14), tongue and tongue base (7), perioral region (8), genian region and periorbital region (5). More than one region was injected in the majority (27) of patients. A 1 ml syringe with an 18 G cannula was used to perform the retrograde layered fat injection. The injected quantities varied between 10 and 35 ml.

There were no major complications recorded during or after the procedure. Minor postoperative edema and pain at the injection site were encountered in all patients. More extended ecchymoses were noted in six patients.

The outcomes were evaluated by clinical and photographic examinations one week, one month, three months and six months after the procedure. Twenty-eight patients had further evaluations at one year and beyond following fat grafting.

- **Surgical outcomes**

At one week the most obvious improvement was regarding tissue filling, with good restoration of facial symmetry in all the cases presenting with this complaint. The augmented volume of the reconstructed regions was noticeable in all patients at seven days after the procedure. The volume was maintained at three and six months after surgery in 29 patients. Only in three cases, there was a slight decrease in the previously obtained soft tissue augmentation at three and six months. All three patients had had previous radiotherapy. In 26 of the included cases multiple autologous fat grafting sessions were needed to reach the desired outcome.

The postoperative scar aspect significantly improved in all patients with retractile scars, at three and six months after fat grafting, together with functional improvement regarding increased tissue mobility. A decrease in local pain at three months after the grafting procedure was noticed by all patients with this initial complaint. Deglutition improvement was noticed immediately after the procedure in patients with this initial complaint. No relevant correlation could be established between the method of harvesting and processing and the post-injection outcomes. There were no tumor recurrences during the follow-up period.

The favorable outcomes are exemplified by two cases (Fig 2.4.1-2.4.5).

Fig.2.4.1. Example 1: Patient with adenoid cystic carcinoma of the right parotid gland before tumor removal.

Fig. 2.4.2. Example 1: Clinical aspect of the patient 3 years after tumor removal, demonstrating the presence of the retromandibular depression.

Fig. 2.4.3. Example 1: Aspect of the patient one year after one session of autologous fat grafting in the right parotid region showing local volume restoration.

Fig. 2.4.4. Example 2: Clinical aspect of a patient 2 years following the removal of an extended basal cell carcinoma of the right genian region reconstructed using a lateral pedicled frontal flap. The image demonstrates the presence of unaesthetic postoperative scars and the depressed right genian region

Fig. 2.4.5. Example 2: Clinical aspect of the same patient one year after autologous fat grafting in the right genian region showing the augmented volume and softened aspect of the postoperative scars

2.4.3 Discussions

There are controversies surrounding the subject of autologous fat grafting for reconstructing oncologic defects. Some authors raised concern over the possibility of stimulating local tumor recurrence by the injection of adipose tissue in oncologic patients, considering the regenerating properties of the mesenchymal stem cells contained in the grafted fat. Nevertheless, most studies did not find an increased rate of local recurrence following fat grafting in oncologic patients (Rigotti et al., 2010; Kaoutzanis et al., 2016; Groen et al., 2016). In our case series, there were no cases of local recurrences during the follow-up period. To avoid camouflaging a possible local recurrence, we performed the fat grafting procedure following a time interval of minimum one year after the tumor resection surgery. In addition, imaging was used in all the included cases for excluding local and distant recurrence prior to autologous fat grafting. Other authors also recommend performing imaging evaluation before and after lipofilling, including the biopsy of suspicious lesions, in addition to increasing the time interval between tumor resection and autologous fat grafting, particularly in cases of locally advanced or histologic aggressive malignancies (Ho Quoc et al., 2015; Kaoutzanis et al., 2016; Groen et al., 2016).

Studies have shown that soft tissue quality is greatly improved in irradiated areas by performing autologous fat transfer (Rigotti et al., 2007; Garza et al., 2014; Borrelli et al., 2019). The structural changes associated with fat grafting are due to the increase in the hydration of the soft tissues, but also due to the presence of neovascularization and stimulated local regeneration, processes that are mediated by the adipose-derived stem cells (Rigotti et al., 2007; Garza et al., 2014). One study showed that although the quality of the irradiated soft tissues increased following fat grafting, the amount of grafted fat integration was decreased in patients with previous radiotherapy (Garza et al., 2014). In our study, we found an increase in tissue quality after autologous fat grafting in all patients, including the ones with a history of radiotherapy. Although all patients in which the volume of injected fat slightly decreased at six months after fat grafting had previous radiotherapy, this was not definitory for all patients, since there were other cases in which the volume remained constant despite of radiotherapy history.

Another issue in performing autologous fat grafting in oncologic cases is that the quantity of fat available for harvesting in one session may be limited due to the debilitating nature of the primary disease. In this regard, there are obvious concerns for patients with operated oral cancers and difficulty swallowing, which often translates into the need to perform multiple injection sessions to reach the desired outcome. Furthermore, some defects require increased amounts of adipose tissue for filling, endangering the integration of the grafted fat, particularly in irradiated terrain with increased fibrosis and decreased vascularity (Garza et al., 2014; Hammond et al., 2019). To minimize the risk of fat resorption, multiple lipofilling sessions can be planned in important volume deficiency for administering the total amount of desired volume, thus also decreasing concerns regarding the fat availability in oncologic patients (Karmali et al., 2018; Clauser et al., 2019). Similarly, in our case series, multiple injection sessions were performed in more than three quarters of the included patients in order to reach the final desired outcome.

There are multiple benefits of autologous fat grafting for the rehabilitation of defects following head and neck cancer surgery. In our opinion, one of the most useful applications is improving the aesthetic and functional outcomes of free flap reconstruction. The advantages of using autologous fat transfer for enhancing results following radialis free flap reconstruction have also been mentioned by Longo et al. (Longo et al., 2019). In addition to improving appearance in cases of facial skin reconstruction using flaps, we used fat grafting with favorable results for augmenting the volume of reconstructed tongue defects in order to improve deglutition. In our experience, this allows overcoming the disadvantages of using the thin radialis free flap for near-total tongue reconstruction. Additionally, autologous fat transfer is also useful in cases of tongue reconstruction using musculo-cutaneous flaps, in which the initial volume is gradually lost due to the atrophy of the muscular component of the flap. Although the benefits of lipofilling for head and neck volume augmentation have been well documented by many authors (Krastev et al., 2018; Clauser et al., 2019), there is an increased need for further studies focusing on tongue rehabilitation using autologous fat grafting. Navach et al. achieved favorable outcomes by injecting adipose tissue in the tongue base of a patient with radiotherapy history and dysphagia for improving deglutition (Navach et al., 2011). Similarly, we also achieved favorable functional outcomes since deglutition improved after fat grafting in all patients initially complaining of dysphagia.

Face and neck contour deformities following tumor resection and reconstruction can be improved by autologous fat grafting. The volumizing and regenerative features of the adipose tissue are underlined by many authors (Clauser et al., 2011; Krastev et al., 2018; Longo et al., 2019). In our study we achieved good aesthetic and functional outcomes in the rehabilitation of reconstructed defects following the curative treatment of malignant tumors with different locations and reconstruction methods, including filling defects after the removal of parotid malignancies, skin, lip and oral malignancies. The submandibular and cervical regions were also filled in patients with associated neck dissection performed at the same time with tumor removal. Multiple regions were injected in the majority of patients with good outcomes regarding volume restoration and scar softening.

The filling property of the adipose tissue helps restore the volume of the region, while the regenerative attributes rendered by the adipose-derived stem cells improve soft tissue quality, soften the aspect of postoperative scars, offer mobility of the tissue layers, and could even be responsible for the described analgesic effect of the grafted fat (Negenborn et al., 2016; Riyat et al., 2017). Mechanical factors related to the injection technique may contribute to pain release, since the local scar tissue is separated from subjacent soft tissues by cannula movement and adipose tissue injection. The added fat layer then separates the superficial and deep soft tissues and acts like a cushion that helps increase the mobility of the tissues. In addition, the analgesic effect is also attributed to the anti-inflammatory substances released by the adipose-derived mesenchymal stem cells contained in the grafted fat (Riyat et al., 2017). Like the findings of other authors (Huang et al., 2015; To et al., 2019), we also found positive outcomes regarding both scar softening and pain relief, in all patients initially presenting with such complaints.

Concluding remarks

In our experience, autologous fat grafting rendered safe, positive outcomes in the functional and aesthetic rehabilitation of various defects following oncologic surgery in the head and neck regions. Volume augmentation, tissue quality improvement, scar release and pain reduction are some advantages of using autologous fat grafting in improving reconstructive outcomes in oncologic patients for an increased life quality.

CHAPTER 3.
MINIMALLY INVASIVE APPROACHES IN SALIVARY GLAND PATHOLOGY

3.1. STATE OF THE ART IN MINIMALLY INVASIVE SURGERY FOR SALIVARY GLAND PATHOLOGY

Minimum disruption of the normal anatomy and physiology of the salivary glands is essential in order to maintain their function. In the present times, more gland preserving procedures are described and preferred to the classic approaches often involving sialadenectomy. Additionally, when gland removal is unavoidable due to the presence of a neoplastic condition, the least invasive techniques are indicated for the surgical removal, as well as for the treatment of postoperative sequelae, in order to avoid further scarring (Yu, Peng, 2019).

The parotid and the submandibular gland have important contributions to maintaining normal human appearance and social behavior at the same time with function. Their role is primarily functional, since they ensure the majority of salivary secretion which participates in tissue lubrication, food digestion and the formation of food bolus, among other contributions, including the local immunologic defense role (Porcheri, Mitsiadis, 2019). Xerostomia is a known determinant for significant oral discomfort, as well as associated with local injuries, infections, dental problems, all determining the impossibility of performing proper mastication and deglutition. In addition to their significant functional role, changes in their volume or their surgical absence influences facial contour and appearance with consequences on self-perception and social interactions. Furthermore, the parotid gland provides protection for the facial nerve coursing through it (Carlson, 2000; Porcheri, Mitsiadis, 2019). The exposed facial nerve following parotidectomy is more vulnerable to injury. Secondary surgeries in this area also increase the risk of nerve injury due to the presence of fibrous tissue.

Among the multiple complications that may be encountered in major salivary gland removal surgery or posttraumatic lesions of the salivary glands, we mention the injury of several nerves, salivary fistula formation, Frey syndrome (Springborg et al., 2013; Chiesa Estomba et al., 2019). The occurrence of such complications can significantly impact the patient’s life quality. Minimally invasive procedures are required for functional and appearance improvement, therefore avoiding further injury by open surgery.

3.1.1. Minimally invasive approaches to posttraumatic salivary gland pathology

Most traumatic-related sequelae involve the parotid gland, with only exceptional cases affecting the submandibular gland (Jana et al., 2006). A layered suture with tight closure of the glandular capsule are the known recommendations for acute posttraumatic lacerations involving the parenchyma of the parotid gland. In addition, duct injuries as well as facial nerve injuries should be detected in the acute setting and direct anastomosis attempted (Van Sickels, 2009; Gordin et al., 2010). However, there are cases in which this initial treatment is not effective, or the injury was not discovered during primary wound exploration with absence of initial treatment, resulting in the formation of a salivary fistula. Treating this complication can prove especially difficult with classic methods ranging from the surgical removal of the fistulous tract to sialadenectomy, or even radiotherapy for inducing glandular atrophy (Akinbami, 2009; Van Sickels, 2009; Christiansen et al., 2009). Over time, the benefits of botulinum toxin administration in traumatic injuries of the salivary glands became apparent, in an attempt to avoid the more aggressive classic treatment approaches. It is also effective as a prophylactic method to avoid the formation of the salivary fistula (Graillon et al., 2019; Serrera-Figallo et al., 2020).

Other minimally invasive approaches for the temporary suppression of the salivary flux in order to avoid the formation or allow the closure of the fistulous tract involve scopolamine administration via transdermal plasters (Gallo et al., 2013; Mantsopoulos et al., 2018). However, complications can sometimes occur by the inadvertent use of the plasters, or by interaction with other drugs, leading to anticholinergic poisoning (Zhang et al., 2017). The absorbed substance inhibits not only the function of the affected salivary gland, but of all salivary glands, leading to hyposialia and its unpleasant outcomes on oral hygiene and possible increased risk of caries development, as well as oral and salivary gland infections (Galili et al., 2019). In contrast, botulinum toxin only suppresses the salivary function of the gland in which it is administered, therefore it is not associated with an overall decreased salivary flux and avoids the previously mentioned complications. In complicated cases of salivary fistulas, the association of scopolamine administration with local botulinum toxin injections was described with good outcomes (Dessy et al., 2007).

Other sequelae of salivary gland trauma involve facial nerve injury, retractile scar formation and facial asymmetry, as well as chronic local pain. Facial nerve injury can be addressed by minimally invasive techniques aimed at repositioning the ptosed tissues, considering the level of the injury. Suture suspension can be effectively employed in this regard. Additionally, botulinum toxin can aid in camouflaging the defect and restoring facial symmetry by injecting it on the contralateral side (Serrera-Figallo et al., 2020). For improving the quality of the soft tissues and softening local scars, at the same time with local pain reduction, autologous fat grafting can be performed (Huang et al., 2015; Negenborn et al., 2016).

3.1.2. Minimally invasive approaches to obstructive salivary gland pathology

Retrieving salivary calculi via the ductal system under an endoscopic view, fragmenting the sialoliths by extracorporeal lithotripsy or intraductal laser fragmentation, as well as sialolithotomy are all procedures that are minimally invasive and avoid salivary gland excision (Lafont et al., 2018; Guastaldi et al., 2018; McCain, Montero, 2018). Each of those procedures can be performed alone or in association with another technique, and different imaging techniques can be added for enhancing results (Guastaldi et al., 2018; Gillespie, 2018). There are certain main indications, as well as risks for each procedure, but their main advantage is ensuring gland preservation and functional rehabilitation (Foletti et al., 2016).

Many studies evaluate the benefits of sialendoscopy as a minimally invasive technique used for the diagnosis and treatment of obstructive disorders of the salivary glands. Its diagnostic value is highly emphasized by many authors, since radiotransparent calculi can also be detected, as well as ductal stenosis, thus avoiding the need for sialography (Kondo et al., 2018). In addition, when the anatomical conditions and the dimensions of the sialoliths allow it, treatment can be attempted in the same session, following diagnosis (Kopeć et al, 2016; Kondo et al., 2018). Nevertheless, performing this procedure is quite time consuming and requires special equipment that is expensive and not available in the majority of offices (Kopeć et al, 2016; Foletti et al., 2016). Furthermore, great skill and experience are required for achieving best results, which are built in a long learning curve (Carta et al., 2017), with some studies even describing the use of 3D printed models of the salivary ducts to aid the training of surgeons (Canzi et al., 2020). In addition, the use of sialendoscopy does not offer many advantages over sialolithotomy for calculi of large dimensions, that must be initially fragmented, which carries inherent risks of complications (Foletti et al., 2016). Therefore, sialolithotomy is still preferred and primarily used by the many surgeons, with continuous technique refinements and intents to further expand the indications in the interest of gland preservation (Koch et al., 2009; Guastaldi et al., 2018; Saga-Gutierrez et al., 2019).

Performing the minimally invasive intraoral removal of the salivary calculi by sialolithotomy allows the avoidance of sialadenectomy in many cases of ductal salivary lithiasis. The procedure can be performed in an office setting under local anesthesia, which further decreases the overall risks (Foletti et al., 2016). Although some calculi located in the salivary gland duct can be approached with confidence via an intraoral route, like the ones located at the level of the papilla or distal segment of the main duct (McCain, Montero, 2018), there is concern over performing sialolithotomy for sialoliths located in more complex anatomical regions, like the submandibular gland infundibulum or proximal segment of Stensen's duct (Foletti et al., 2016; Saga-Gutierrez et al., 2019). The confidence of surgeons in approaching such difficult cases is increased when the exact location of the sialolith can be accurately determined prior to surgery, when landmarks can be determined for a controlled access, and therefore the established preoperative plan allows a well contoured picture of the intraoperative setting (Kondo et al., 2018).

The indication for the intraoral removal of salivary stones is therefore greatly expanded by using imaging techniques to accurately determine the number and precise location of the salivary stones, in order to ensure a targeted, safe and quick removal. CBCT (Cone Beam Computed Tomography) is not routinely used for the assessment of salivary gland disorders. However, it becomes an important tool in the diagnosis and management of salivary gland lithiasis (Dreiseidler et al., 2010; van der Meij et al., 2018).

This imaging modality is widely available to maxillofacial practice offices and surgeons are well accustomed to assessing the obtained images. One advantage of using CBCT is the possibility to visualize the individual anatomy of the patient by using a three-dimensional reconstruction of the images, thus creating a spatial preview of the surgical setting, while also ensuring the possibility to determine useful anatomical landmarks to find the sialolith intraoperative in relation to adjacent structures (Dreiseidler et al., 2010; van der Meij et al., 2018). In addition, one major advantage is that it can be performed in the day of the surgery, with the patient seated, the same position used for the sialolitotomy, therefore the migration of the sialolith is minimized before surgery.

3.1.3. Minimally invasive approaches for the prevention and management of sequalae following salivary gland tumor removal

Sialadenectomy for salivary gland tumor removal is associated with possible complications and sequelae which range from mild to severe depending on the salivary gland involved and the type and extent of surgery. Soft tissue volume deficiency causing facial asymmetry and nerve injuries are some of the most common encounters that can cause a significant decrease in the patient’s quality of life (Cummins et al, 2020). In the event of such complications, minimally invasive procedures may help partially restore the appearance and function and improve the patient’s comfort.

The occurrence of complications can be minimized by technique modifications. All aspects of the procedure contribute to the final outcome, starting with the incision. In this regard, studies have shown the importance of a minimally invasive access for the removal of benign parotid gland tumors by using smaller incisions, hidden in the natural skin creases or less obvious anatomical regions, like the facelift approach. This results in a more natural outcome with inconspicuous scars (Yu, Peng, 2019; Cummins et al, 2020). Another significant factor that greatly contributes to the aesthetic and functional outcome is the method of plasty for the post parotidectomy defect. Although myoplasty using the sternocleidomastoid or the digastric muscles is traditionally used, the interruption of these muscles may be associated with increased postoperative pain and even movement restriction due to the formation of scar tissue, since the muscles are involved in usual movements (Manola et al, 2018; Ye et al, 2019). Additionally, muscle atrophy that occurs in time can make the volume deficit in the parotid region more apparent. The superficial musculoaponeurotic system (SMAS) flap offers a good alternative for defect plasty, since it can be safely dissected of the parotid tissue in cases of benign tumors and it is usually present in excess due to the progressive tumor growth that expanded the superficial tissues including the overlying SMAS and skin. It can be folded into the defect to compensate for the volume deficit, while also ensuring an effective tissue barrier, thus preventing the onset of Frey’s syndrome (Yu, Peng, 2019).

Even with the best planning and technique, in some instances, complications still occur after parotidectomy. Studies have shown that the integrity of the SMAS is a significant factor in avoiding Frey’s syndrome, since accidentally produced dissection holes in its surface have been linked to limited skin areas with focal hyperhidrosis and congestion during meals (Hayashi et al., 2016). However, this complication can be effectively managed by local botulinum toxin injections (Serrera-Figallo et al., 2020). Other common complications following parotidectomy can also be managed by the minimally invasive botulinum toxin administration, such as postoperative salivary fistulas and sialocele formation (Maharaj et al., 2020). Sialocele development and oro-cutaneous fistula formation that rarely follow submandibular gland surgery (Erbek et al., 2016) can also be addressed by means of suppressing salivary secretion using botulinum toxin.

In the case of malignant salivary gland tumors, postoperative sequalae cannot always be avoided due to the need for more extensive tissue removal. Facial nerve preservation is the most important functional aspect of parotid gland surgery. In the presence of malignant tumors, its complete preservation is often not possible, considering the necessity of ensuring tumor free margins. Primary or secondary nerve reconstruction is advisable whenever possible, but usually requires complex prolonged procedures, performed under general anesthesia, with increased overall morbidity (Razfar et al., 2016). In elderly patients with multiple comorbidities, in patients reluctant to undergo another major surgery, or even to bridge the time until the nerve reconstruction is performed, minimally invasive static reanimation techniques can help decrease the debilitating sequelae of facial nerve paralysis (Choe et al., 2017). In this regard, the insertion of soft tissue suture suspension by barbed threads is easily performed under local anesthesia. The procedure may be repeated until the desired outcomes are achieved, and it can be associated to other minimally invasive techniques performed under local anesthesia, like the insertion of a gold weight in the superior eyelid, or autologous fat grafting. These procedures improve soft tissue positioning by correcting the position of the inferior eyelid and eyelid closure, lifting the oral commissure, and providing increased tonus of the cheek muscles, thus decreasing ocular complications, while also having a positive impact on mastication, deglutition and phonation (Leach et al., 2017).

Autologous fat grafting is a minimally invasive procedure that can be performed under local anesthesia for improving the outcomes of salivary gland surgery. It contributes to reducing the aesthetic sequelae of parotidectomy or submaxillectomy by filling the postoperative defect in order to restore facial symmetry (Clauser et al., 2019). In addition to the filling effect of the grafted adipose tissue, the contained adipose-derived stem cells improve the quality of the local tissues and postoperative scars, while also decreasing postoperative pain (Huang et al., 2015; Negenborn et al., 2016). Thus, the procedure can greatly improve sequelae following cancer surgery and radiotherapy (Borrelli et al., 2019).

3.2. THE BENEFITS OF BOTULINUM TOXIN USE IN SALIVARY GLAND PATHOLOGY

The effects of botulinum toxin on the modulation of salivary flow are well-known, but the necessary dosages for a desired outcome and the additional effects on the glandular parenchyma are less investigated. Due to the rarity of salivary fistulas, there are few studies including small numbers of patients and different types of toxin used, various dosages and infiltration patterns. Also, they do not differentiate between the particularities of posttraumatic versus postoperative fistulas. Surgical treatment for treating salivary fistulas is invasive and does not always lead to successful outcomes (Lovato et al., 2017). Radiotherapy that was used in the past for producing glandular atrophy is no longer recommended due to its debilitating complications. Botulinum toxin offers a good alternative to open procedures, since it is non-invasive and with few to no complications.

Botulinum toxin (BT) is a well-known modulator of salivary secretion. Its action on the glandular parasympathetic neurosecretory synapses blocks the release of acetylcholine, resulting in a decrease in salivary production. Although there are many publications describing the use of botulinum toxin for sialorrhea (Lakraj et al., 2013), there are fewer articles focusing on salivary fistula treatment (Lovato et al., 2017) and even less describing the use of botulinum toxin for post-traumatic fistulas unrelated to surgery (Arnaud et al., 2008). This is due to the scarcity of cases presenting with salivary gland or duct injury unresponsive to the initial surgical and conservative measures.

Although rare in occurrence, salivary fistulas are a debilitating condition for the patient, affecting the social life, limiting public outings. In a traumatic context, it adds to the unpleasant psychological outcome determined by the presence of the facial scar. The surgical treatment of the condition implies a prolonged hospital stay and therefore increased costs. An effective non-surgical management would be more beneficial and botulinum toxin use offers such an alternative. Due to the small number of posttraumatic cases described in the existing literature, there is no consensus over the selection of the type of botulinum toxin, the most appropriate dose, location and number of injection administration (Arnaud et al., 2008; Lovato et al., 2017).

One focus of our research is the use of botulinum toxin in modulating salivary flow, with beneficial outcomes on the treatment of posttraumatic and postoperative salivary fistulas. The results achieved so far are described in the following original manuscript:

- ✓ Costan VV, Dabija MG, Ciofu ML, Sulea D, Popescu E, Boisteanu O. A functional approach to posttraumatic salivary fistula treatment: the use of botulinum toxin. J Craniofac Surg 2019;30(3):871-875.

The objective of the study was to present the author's experience regarding the management of non-surgical trauma-related salivary fistulas of the parotid gland by the off-label use of botulinum toxin injections. We also aimed to outline the differences between postoperative and posttraumatic salivary fistulas and their relevance on establishing the treatment plan.

3.2.1. Materials and method

We reviewed the medical charts of patients in our institution between January 2013 and December 2017. We included only patients with post-traumatic salivary fistulas that were treated by botulinum toxin injection. The general patient information, the traumatic mechanism, topography and characteristics of the wounds, the previous treatments, the indication for neurotoxin administration, as well as the injection technique and outcomes were all documented.

3.2.2. Results

- **Clinical characteristics**

Over a period of five years, six cases of post-traumatic parotid fistulas were treated by botulinum toxin injection. The patients were all male, aged between 18 and 51. They initially presented for trauma-related facial lacerations. The traumatic mechanism involved two cases of circular saw injury, two grinder wheel injuries, one broken glass injury, and a penetrating cow horn injury. An associated lesion of the facial nerve was diagnosed in two patients and a mandibular fracture in one patient.

Three of the wounds were complex, involving several facial areas, including the parotid-masseteric region. Another complex beveled laceration was in the genian region (Fig. 3.2.1.). Two patients presented with relatively small wounds located over the topography of the parotid-masseteric region in one case (Fig. 3.2.2.), and at the inferior aspect of the nasal-genian fold in the second patient.

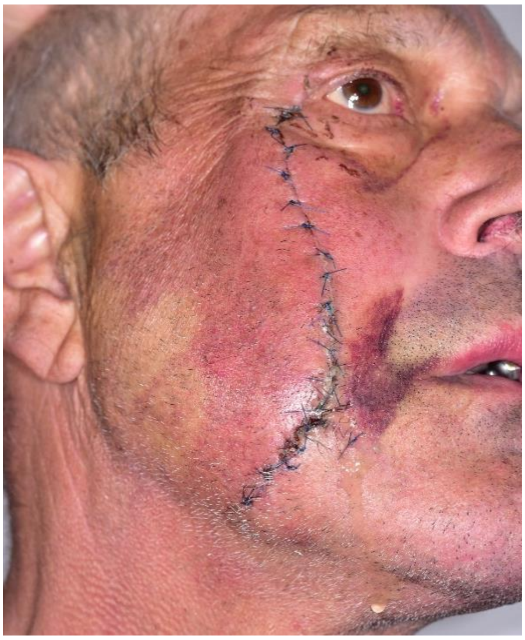

Fig. 3.2.1. Patient with posttraumatic salivary fistula due to a complex beveled wound in the genian region

Fig. 3.2.2. Patient with posttraumatic salivary fistula due to a small penetrating wound in the parotid-masseteric region

Exploration of the wounds revealed involvement of the parotid glandular tissue in three cases of complex facial lacerations. The parotid duct was cannulated using an epidural catheter and methylene blue was injected retrograde, but no injury of the duct was found. A layered closure of the wounds was performed with suturing of the parotid fascia and SMAS layer. A drainage was left in place and was maintained for three to five days. The external end of the gravitational drainage was placed at the inferior aspect of the wound in two cases and in one case a suction drain was exteriorized in the lateral cervical region. Conservative measures were introduced for the prevention of salivary fistula formation. Subcutaneous atropine was administrated in doses of 0.5 mg, 30 minutes before each of the three main meals. Pressure dressings over the parotid region were performed in all cases for one week postoperative during hospital stay.

In the two patients presenting with small lacerations and one patient with a complex laceration located in the genian region, the initial treatment consisted of immediate suturing of the wound without drainage placement. A parotid parenchyma or duct injury was not initially recognized, and patients were not admitted in the hospital. There were no additional conventional recommendations regarding the prevention of salivary fistula formation.

The cutaneous salivary fistula was diagnosed in between one and two weeks after the initial wound closure. The location of the fistula was in the submandibular area in one patient, in the lateral cervical region in one case, in the genian region in one case, at the level of the nasal-genian fold in one patient, in the parotid region for one patient, and in the external auditory canal for another patient.

In one patient with a stabbed nasal-genian wound and one patient with a crushed beveled laceration in the genian region there was reason to suspect a Stensen’s duct injury, considering the trajectory and character of the laceration. The patients opted for a non-surgical treatment.

Botulinum toxin injections were performed in all included patients in the same day of the diagnosis of parotid salivary fistula onset.

- **Therapeutic approach**

The landmarks for the injection area were initially marked. We considered the approximate topography of the parotid gland and duct in an area delineated by the following lines: an anterior superior line tangent to the inferior border of the zygomatic arch, a posterior superior line going from the inferior tragus to the tip of the mastoid, a posterior inferior line following the anterior border of the sternocleidomastoid (SCM) muscle towards the mastoid tip and an anterior inferior line tangent to the anterior border of the masseter muscle.

Palpation was used to determine the bone and muscle landmarks. The masseter anterior border was palpated during forced occlusion. The SCM anterior border was determined with the head rotated to the opposite side and slightly tilted downwards, on a line from the medial clavicle to the mastoid. The anterior limit of the parotid tissue was marked approximately at the middle of the distance between the posterior border of the mandible and the anterior margin of the masseter. Anterior from this line, the parotid duct usually exists the glandular tissue. The height of duct emergence was considered in the area comprising 1.5 cm above and below a line going from the inferior part of the tragus to the oral commissure (Stringer et al., 2012), in between the mid-masseter and anterior-masseter lines, equivalent to the middle third of the tragus-commissure line.

These landmarks were used to evaluate the location of the parotid gland and duct, and thus to determine the best suited location for the botulinum toxin injections.

For the treatment of all salivary fistulas we used Dysport® (Abobotulinum toxin type A, Ipsen Limited, Slough Berkshire, UK). The reconstitution was performed by adding 5 mL of 0.9% sodium chloride solution to the 500 Units Dysport® vial, reaching a dilution of 100 U/mL, equivalent to 10U/0.1mL.

Syringes of 1ml with a detachable 27 G 19 mm long needle were used for the injection. The injections were administered without previous local anesthesia, after skin antisepsis using alcohol in the target area. In the four patients with parenchyma injury the injections were performed aiming for the involved glandular tissue surrounding the scar, over the projection of the gland.

The dose administered for parenchyma injuries was 100 U (1 mL) of Dysport® distributed into six injections administered on both sides of the scar in one session, at a maximum distance of approximately 1 cm from the wound and ensuring less than 1.5 cm in between the injection points, considering the diffusion of the botulinum toxin, attempting to cover most of the surrounding injured glandular tissue. In the two cases of possible Stensen's duct injury, a total dose of 150 U (1.5 mL) of Dysport® was administered into roughly 10 injections spread over the topography of the parotid gland, unrelated to the topography of the wound (Fig. 3.2.3., Fig. 3.2.4.).

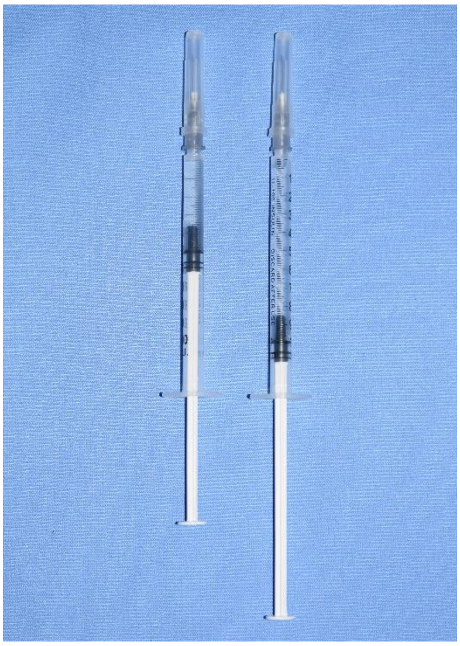

Fig. 3.2.3. Representation of the injection quantity of 1.5 ml equivalent to 150 U (dilution 100 U/ml)

Fig. 3.2.4. Injection technique and markings for a posttraumatic salivary fistula

The depth of the injection was adapted to the individual build of the patient, delivering the botulinum toxin into the parotid tissue. The patient was instructed to contract the masseter muscle to better approximate the depth of the injection by muscle palpation. Increased resistance is felt upon needle insertion when the needle reaches the contracted masseter muscle, indicating the need for needle withdrawal by 2 mm to position it into the overlying parotid tissue.

The admitted patients were discharged from the hospital the same day of botulinum toxin administration with the recommendation of periodic controls at three days, one week, two weeks, one month, six months and twelve months. The ambulatory patients had the same indications regarding follow-up visits after botulinum toxin administration. No additional conservative measures were undertaken.

The subjective salivary flow at the fistula opening was rated in comparison to the pre-injection flow, at three days, one week and two weeks after the botulinum toxin injection.

- **Injection outcomes**

The gradual reduction in salivary flow was noticed starting with day three and continued, as observed in day seven. Complete resolution of the salivary flow at the fistula orifice was obtained at two weeks following the injection in all cases. Controls performed at one month, six months and twelve months confirmed the healing of the salivary fistula and the maintenance of the results. There were no cases of infection or salivary collections during the interval until complete onset of Botulinum toxin effect.

None of the patients needed additional Botulinum toxin injections or subsequent surgery. There was no need for associated conservative measures such as pressure dressings, antisialogogues or suppression of oral intake. Patients had a normal diet following the injections. No adverse effects were declared by the patients regarding xerostomia, mastication, deglutition or facial muscle weakness.

3.2.3. Discussions

Controlling the diffusion of the botulinum toxin is one of the key factors in achieving the desired outcome while minimizing side effects. The balance is maintained when the botulinum toxin type is purposely selected in knowledge of its characteristics and used in the conditions where it would lead to maximum benefit. The exact diffusion is difficult to quantify and there are differences in opinion regarding the contributing factors. Still, an increased diffusion of the botulinum toxin has been linked by some studies to a smaller molecular weight, increased volumes of administration and higher doses (Ravenni et al., 2013). For this purpose, we used Dysport® (Abobotulinum toxin type A, Ipsen Limited, Slough Berkshire, UK) that has a smaller molecular mass ranging from 300 to 900 kDa, as opposed to Botox® (Onabotulinumtoxin type A, Allergan, Inc., Irvine, California, USA), with a fixed 900 kDa molecular mass. When aiming for "chemical parotidectomy" the increased diffusion of the botulinum toxin ensures more coverage of the glandular parenchyma with fewer injections and lower quantities of toxin. This desiderate is contrary to cosmetic procedures where precision is key in targeting only certain facial muscles, while sparing others and minimizing side effects. A conversion ratio between Dysport® and Botox® of 3:1 is stated by most authors to be most accurate in achieving similar effects (Ravenni et al., 2013; Scaglione, 2016). Although it is very difficult to quantify the exact spread of the toxin from the injection site, most injectors consider that the substance diffuses for approximately 1 cm and use this to protect important anatomical structures during cosmetic injections with good results (Niamtu, 2003). We considered the same distance in ensuring uniform spread of the botulinum toxin in the glandular parenchyma by performing the injections at maximum 1 cm from the wound margins when the wound crossed the parotid region, and spacing the injections at maximum 1.5 cm, therefore ensuring a small overlapping to avoid untargeted glandular tissue.

We did not increase the volume of injection by increasing the dilution for the same total dose because, even though the substance diffusion would increase as stated by previous studies (Ravenni et al., 2013), it would be difficult to control and ensure that the substance does not cross the relatively small parotid area leading to undesirable effects on the mimetic or masticatory muscles.

The total dose used for parenchyma injuries in our study was similar to the one administered for cosmetic procedures- 100 U of Dysport®, equivalent to approximately 33 U of Botox®. Slightly higher doses were administered for Stensen's duct injury- 150 U of Dysport®, equivalent to 50 U of Botox®- with the purpose of achieving the functional silencing of the entire parotid gland, as opposed to parenchyma injury when only the severed tissue around the trajectory of the wound needed functional suppression. There is no consensus among authors regarding the most appropriate dose for achieving salivary blockade. Arnaud et al. (Arnaud et al., 2008), in a study concerning posttraumatic salivary fistulas, targeted an aggressive salivary suppression by using 100 U of Botox® equivalent to 300 U of Dysport®. Guntinas-Lichius and Sittel (Guntinas-Lichius, Sittel, 2001) inject 100 U of Dysport® for treating a postparotidectomy fistula. Doses as small as 10 U of Botox® equivalent to 30 U of Dysport® were described for the treatment of a post-parotidectomy salivary fistula by other authors (Marchese-Ragona et al., 2006; Lim, Choi, 2008). Due to the scarcity of cases presenting with trauma-related salivary fistulas, the diversity of clinical scenarios, and individual differences in the volume of the parotid glands, a statistic study evaluating the most appropriate total dose is not feasible. Nevertheless, an initial attempt of injecting smaller doses is possible, since re-injection can be performed at any time for completing the results.

In parenchyma lacerations, the location of toxin injections is important since unnecessary injections in the glandular tissue at a greater distance from the actual injury, do not benefit fistula closure, but raise the total dose of botulinum toxin. Some studies using botulinum toxin for the treatment of postoperative fistulas describe injections around the fistula opening (Ellies et al., 2004; Lim, Choi, 2008). The described postoperative fistulas were overlying the parotid area in all cases and justified the selected injection points. However, the parotid parenchyma fistulas in our study were mostly expressed inferiorly, at the level of the pre-existing drainage, in areas not overlying the parotid gland. The actual place of parotid parenchyma injury was higher. For this reason, the botulinum toxin injections were not administered around the fistula opening in all cases, but around the scar overlapping the parotid topography. The markings of the location of the parotid gland and duct areas were established in relation to the known anatomical landmarks for determining the best location for the injections (Stringer et al., 2012; Toure et al., 2015). In the one case of salivary fistula located in the external ear canal, the injury pattern explained the unusual opening of the fistula. The convex trajectory of the wound, as well as the presence of a cartilage defect in the anterior wall of the external auditory conduct and the location of the deep glandular injury anterior to the external auditory canal, favored the formation and opening of the fistula towards the ear canal.

The depth of the injection was variable, depending on the general build of the individual, considering the perceived thickness of the subcutaneous adipose tissue layer. Intermediate depth was intended, aiming for the glandular tissue, while avoiding intramuscular injection by instructing the patient to contract the masseter muscle during the procedure. Intramuscular injection would lead to the undesirable effect of muscle weakness and volume reduction leading to facial asymmetry, but, not lastly, to the absence of full effect on the parotid glandular tissue and salivary fistula persistence.

In cases of a salivary fistula unresponsive to botulinum toxin treatment, the extensions of the parotid glandular tissue outside of the main parotid body (Stringer et al., 2012; Toure et al., 2015) should be evaluated for injury and supplementary botulinum toxin injections should be administered. The tail of the parotid gland is maybe the most exposed extension of parotid tissue vulnerable to injury, since it can stretch for various lengths over the anterior border of the sternocleidomastoid muscle (Stringer et al., 2012). This is a location commonly overlooked when diagnosing posttraumatic glandular tissue injury, and a common location of injury during neck dissection procedures.

Injury to the deep parapharyngeal parotid extension is extremely rare due to the protection offered by the mandibular ramus. Formation of a fistula due to injury in this region is less likely since the deep location and surrounding structures favor the spontaneous joining and sealing of the glandular tissue. In unresponsive fistulas due to injuries in this area, botulinum toxin can be administered by ultrasound guided injection (Lakraj et al., 2013) for a more precise location of the substance and avoiding diffusion to the deep muscles involved in mastication and deglutition.

Additional causes for unresponsiveness could be due to initial insufficient information regarding the trajectory of the posttraumatic laceration. An accentuated beveling of the wound would necessitate adjusting the injection location accordingly, since the location and extent of the deep injury does not always coincide with the cutaneous injury. In wounds crossing multiple areas including the submandibular region, the salivary fistula could also be due to a submandibular gland injury. Although quite rare in a traumatic context, due to the protection offered by the mandible, this occurrence should be considered in cases with unresponsive to the initial intra-parotid botulinum toxin injections.

In our study, the injections were performed by an experienced injector, guided by clinical landmarks only, followed by onset of the chemodenervation in the usual interval known for abobotulinum toxin. Due to the effectiveness of the administration, absence for the need of additional or repeated injections and absence of side effects, we did not consider necessary any imaging guiding for a more exact substance placement. Ultrasound guided injections into the deep lobe have been performed by authors for the treatment of sialorrhea (Lakraj et al., 2013; Alter, Karp, 2017) and could be a solution for silencing the parapharyngeal glandular tissue in cases of injury with this location. One study found that ultrasound guiding is more useful for injections in the submandibular gland, while anatomic landmarks allow enough accuracy for intra-parotid injections (So et al., 2017).

In our experience one session of treatment was enough to lead to the healing of the salivary fistula. Other authors reported cases in which the initial treatment was not followed by a complete resolution of the fistula and reinjections had to be performed to reach the desired outcome. However, the reported cases involved fistulas associated with complex wounds following gunshots or malignant tumor removal and reconstruction (Gok et al., 2015; Ferron et al., 2017). In cases unresponsive to the initial treatment, additional doses can be administered, and the precision of the infiltrations can be improved by using ultrasound (Gok et al., 2015).

The botulinum toxin treatment was initiated after considering all available treatment options. A non-surgical procedure aimed at salivary fistula closure used by some authors involves superficial radiation therapy in the parotid region leading to fibrosis and atrophy of the glandular parenchyma. Due to concerns regarding malignancy development in the radiated territory, this procedure has been replaced in most cases by the administration of botulinum toxin (Marchese-Ragona et al., 2006). Some authors still advocate the use of radiotherapy for refractory salivary fistulas, unresponsive to botulinum toxin injections (Christiansen et al., 2009). Surgical procedures for repairing posttraumatic salivary fistulas include the re-exploration of the wound and performing the layered closure with careful approximation of the parotid fascia and SMAS layer. The surgical exposure of the injured duct followed by repair could be needed when ductal lesions are diagnosed. In chronic fistulas, the surgical removal of the fistula orifice and fibrous tract is performed, followed by a layered closure of the wound. Unresponsive cases can ultimately be treated by performing parotidectomy. Another surgical procedure aimed at stopping salivary secretion is the tympanic neurectomy by interrupting Jacobsen's nerve and achieving parasympathetic denervation of the parotid tissue (Bomeli et al., 2008; Gordin et al., 2010). However, these are procedures with a high morbidity and implying additional hospitalization time, medication and monitoring. When faced with the surgical alternatives, the patients in our study opted for the non-surgical approach. This is consistent with the observations of other authors stating that botulinum toxin treatment has replaced surgical methods for salivary fistula closure in most of cases due to the less invasive character (Arnaud et al., 2006; Gordin et al., 2010).

As opposed to postoperative fistulas involving surgically made incisions and dissection, in fistulas following trauma, the wound pattern is mostly irregular, the depth of injury is variable, the tissues are frequently crushed by the impact force and there could be additional injury to adjacent structures, especially the facial nerve, but also the mandibular ramus and the ear canal. These characteristics make the initial diagnosis of glandular or duct injury and the acute treatment plan difficult to establish, with possible development of salivary fistulas despite the initial management.

Botulinum toxin is also useful in treating salivary fistulas following iatrogenic parotid injury (Marchese-Ragona et al., 2006), but the choice and administering of the treatment differ slightly considering the particularity of the postoperative wound and the initial condition for which surgery was performed. The anatomy of the region is different in post-parotidectomy fistulas following benign or malignant parotid tumor surgery where the superficial glandular tissue is missing in addition to differences in the superficial muscular aponeurotic system anatomy if a plication has been performed for the plasty of the defect, or if a regional muscle was rotated into the defect. In post-parotidectomy fistulas, the residual parotid tissue may be more difficult to inject with precision (Marchese-Ragona et al., 2006; Lim, Choi, 2008). Therefore, these differences should be considered carefully when administering botulinum toxin treatment for established salivary fistulas following surgical trauma, since missing tissues in the parotid region may lead to inaccurate placement of the botulinum toxin in the immediate proximity of muscular structures and occurrence of side effects. Ultrasound guided injections can increase the accuracy of the procedure in such cases.

Another frequent iatrogenic cause is during neck dissection when the inferior process of the parotid gland may be injured, resulting in salivary fistulas that complicate the surgical outcome. In this case, as opposed to posttraumatic fistulas, botulinum toxin may not be necessary if the patient will undergo radiotherapy for the malignancy, which might also resolve the salivary fistula.

Concluding remarks

In our study, botulinum toxin injections were efficient as a single treatment for trauma-related salivary fistulas diagnosed in the first two weeks following trauma. No additional conservatory treatment or surgical treatment was needed. There were no side effects related to botulinum toxin use.

Due to the diversity of wound patterns as well as the multiple anatomical variations of parotid glandular tissue extension and duct projection, an exact standardization of injection sites and doses is not possible, but an understanding of the physiology of glandular injuries and botulinum toxin effects, as well as a good knowledge of the regional anatomy, can help the delivering of accurately placed injections and ensure good results.

3.3. ADVANCES IN THE DIAGNOSIS AND TREATMENT OF SALIVARY GLAND LITHIASIS

Salivary gland lithiasis is a common encounter in maxillofacial surgery. Recent studies advocate the feasibility of glandular preservation by performing sialolithotomy even in difficult cases involving deeply located salivary stones. This desiderate is possible when the location of the calculus can be accurately defined in space and relation to adjacent anatomic structures. CBCT allows an accurate determination of the location, number and shape of the existing sialoliths, while also providing landmarks and measured distances for more effortless intraoperative calculus detection. Both submandibular and parotid duct calculi can be evaluated using CBCT (Dreiseidler et al., 2010; Jadu, Lam, 2013; Van der Meij et al., 2018).

Sialolithiasis stands for the majority of salivary gland disorders. Anatomic, topographic and functional factors contribute to the predominant formation of sialoliths in the submandibular glandular structures in over 80% of cases, mainly in the ductal system, and more often in the proximal section of the duct or hilar area (Harrison, 2009; Zheng et al., 2013; Kraaij et al., 2014; Sigismund et al., 2015).

Preservation of the submandibular gland is important for maintaining the fullness and normal contour of the submandibular area, but also for avoiding the injury of several adjacent nerves. This concept is becoming increasingly accepted since several studies have shown that glandular function is regained after the removal of the salivary stone with few cases of recurrent lithiasis or complications (Makdissi et al., 2004; Woo et al., 2014).

The intraoral extraction of sialoliths can be achieved by sialolithotomy, a technique that avoids the high costs and the long learning curve necessary for endoscopic procedures, and that can be performed in a shorter operating time. Although frequently performed for distally located calculi, the removal of more proximal and hilar sialoliths presents some technical challenges, especially when the calculi are not detectable by bimanual palpation, and it is the main reason why many surgeons still opt for performing submaxillectomy in such cases. Approximately two thirds of the submandibular sialoliths are located in the proximal part of the duct and infundibulum (Kraaij et al., 2014; Sigismund et al., 2015). With such a high frequency, it is important to develop widely accessible techniques to help increase the confidence of surgeons in approaching these calculi by intraoral route and preserve the submandibular gland.

So far, the results of our study regarding the approach of difficult cases of submandibular sialolithiasis by preoperative CBCT diagnosis and planning have been described in an original manuscript:

- ✓ Costan VV, Ciocan-Pendefunda CC, Sulea D, Popescu E, Boisteanu O. Use of cone-beam computed tomography in performing submandibular sialolithotomy. J Oral Maxillofac Surg 2019;77(8):1656.e1-1656.e8.

The objective of this study was to present our experience regarding the intraoral removal of salivary calculi by sialolithotomy, performed under local anesthesia, as an office-based procedure, for both palpable and unpalpable sialoliths.

3.3.1. Materials and methods

We performed a retrospective chart review of all patients with submandibular sialolithiasis who underwent sialolithotomy between January 2015 and January 2018. We only included adult patients who were evaluated by the help of CBCT performed in the day of surgery and had minimum 12 months of follow-up. We selected the patients who had no history of previous surgery in the area. Only patients without indication for submandibular gland removal were included in the study. Patients who underwent sialolithotomy for an acute obstructive episode due to ductal lithiasis, but diagnosed with additional intra-parenchymatous calculi, were scheduled for submaxillectomy one month after the acute episode and were therefore excluded from the study. The general patient information, the method of imaging diagnosis, the surgical technique and the outcomes were all documented.

3.3.2. Results

- **Clinical and imaging characteristics**

A total of 32 patients with submandibular sialolithiasis were included in the study. The mean age of the selected patients was 42 years ranging between 17 and 67. There were 17 men and 15 women. 17 patients declared the presenting episode as the first manifestation of the disease, while the other 15 declared between one and three previous episodes of obstructive symptoms in the last two years that were treated by conservative means only.

CBCT was performed in the day of surgery for all patients. The field included the whole mandible (including the complete vertical branches) and the hyoid bone for a certain containing of the entire submandibular gland area. The presence of a concurrent parotid gland lithiasis can also be evaluated on this volume. Images were analyzed by the help of dedicated software (RadiAnt and Osirix DICOM viewers). Multiple panel view was used for comparison and measuring. A three-dimensional image reconstruction was performed for an enhanced grasping of the anatomy and of the relation with the surrounding structures. The number, location and the dimensions (largest length, width and height) of the salivary calculi were documented, as well as the approximate shape (Fig. 3.3.1.- 3.3.4.).

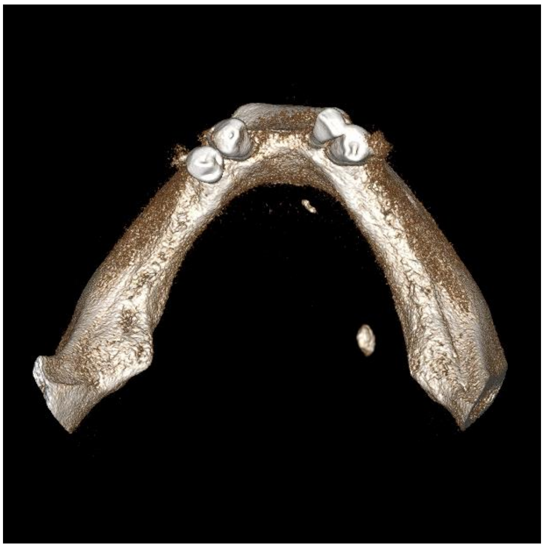

Fig. 3.3.1. Example 1: CBCT reconstruction in a patient with multiple sialoliths located in the proximal and distal parts of the right Wharton's duct (superior view)

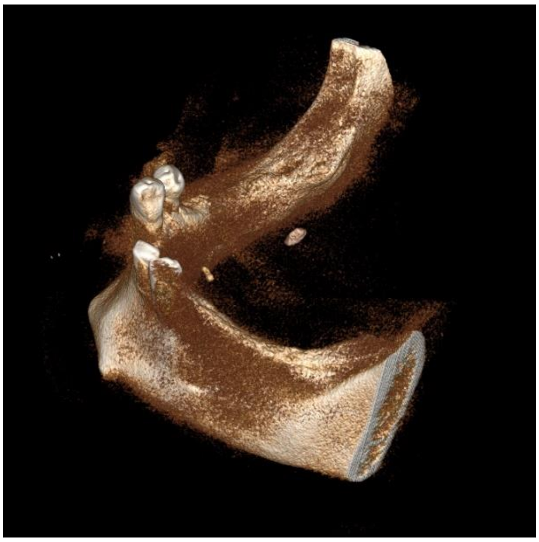

Fig. 3.3.2. Example 1: CBCT reconstruction in the same patient with multiple sialoliths located in the proximal and distal parts of the right Wharton's duct (superior lateral view)

Fig. 3.3.3. Example 2: CBCT reconstruction in a patient with three sialoliths located in the distal half of the left Wharton's duct (superior view)

Fig. 3.3.4. Example 2: The extracted three sialoliths shown after sialolithotomy

Landmarks for the position of the calculi were determined. Most often, the ipsilateral mandibular teeth were used for orientation in distal, middle, and proximal ductal calculi. In the absence of the ipsilateral mandibular teeth, the contralateral mandibular teeth can be used, or even maxillary teeth, although less precise, taking into consideration the approximate relation between the dental arches when the CBCT was performed. In an edentulous patient, the distance can be measured from the midline to a horizontal line passing through the sialolith. The position of the salivary stone in relation to the mental foramen may also be of help. Useful landmarks for hilar calculi are determining the approximate position in relation to the anterior and posterior borders of the vertical mandibular ramus, particularly how far behind the anterior mandibular border. For approximating the depth, the occlusal plane of the mandibular teeth or the alveolar crest plane in edentulous patients, as well as the basilar border of the mandible serve as useful landmarks. The mylohyoid line is another useful structure for determining the position of the hilum and hilar calculi.

Nineteen patients (59.37%) had only one salivary calculus upon presentation. Thirteen patients (40.62 %) presented with multiple sialoliths, from which in 5 patients the multiple calculi were found in the same ductal segment, while in the other eight patients they were distributed in more than one ductal region.

The distribution of the calculi in the ductal segments, including the eight cases with simultaneous calculi found in more than one ductal region, was: 16 cases (50 %) had sialoliths located in the distal section of the Wharton's duct, 10 cases (31.25 %) in the middle section and 14 cases (43.75 %) in the proximal duct or hilar area. In 10 cases (31.25 %) the patients had unpalpable stones, of which in four cases (12.5 %) the sialoliths were in the hilum. No concurrent parotid gland lithiasis was found in the included cases.

The largest diameter of the calculi as measured on CBCT was 7 mm in the distal section, 6 mm for middle portion calculi and 41 mm for proximal and hilar calculi. A total of 51 sialoliths were diagnosed using CBCT. There were five megaliths, defined as sialoliths greater than 1 cm in the largest diameter, all found in the proximal and hilar areas. The smallest diameter was 2 mm for a distal duct stone.

- **Therapeutic approach**

Sialolithotomy was performed with the patient seated in the dental chair, under local anesthesia consisting of a lingual nerve block completed by local infiltration of small quantities of anesthetic with vasoconstrictor in the floor of the mouth. Mild sedation was achieved by the preoperative administration of oral Midazolam, 30 minutes before the procedure.

For distal and middle ductal sialoliths, the approximate location was identified by using the landmarks obtained from the CBCT images and by palpation. An incision was made in the mucosa of the floor of the mouth overlying the calculus, the duct was then identified and incised over the sialolith which was then removed.

For proximal and hilar sialoliths, the mucosal incision extended from the middle to the posterior floor of the mouth. The duct was identified in the anterior aspect of the incision, grasped, and then traced backwards and dissected from the surrounding tissues. The lingual nerve was then encountered, carefully freed and gently tractioned laterally, protecting it during further dissection of the Wharton's duct towards the hilum. The posterior margin of the mylohyoid announced the proximity of the hilum. Landmarks obtained from the CBCT evaluation were used as guides to identify the location of the calculi. The duct was incised over the calculi when they were palpable, or proximally, at the hilum, followed by posterior opening until reaching the calculi, in case of unpalpable salivary stones. Knowledge of the number, size, arrangement, and shape of the calculi was used to ensure complete removal.

At the end of the procedure Wharton's duct was left open, without suturing the surgically made opening to the oral mucosa, nor direct closure of the duct. We did not suture the mucosa of the floor of the mouth. An iodoform gauze was inserted into the surgical wound with the purpose of keeping the wound margins open, ensuring drainage, and offering protection for secondary healing for one week.

The patients had recommendations of antibiotic and anti-inflammatory treatment for seven days after surgery. Subsequent appointments for reevaluation took place at three months, six months and one year following sialolithotomy.

- **Surgical outcomes**

The number of surgically extracted calculi was identical to the one found upon CBCT evaluation. One megalith fragmented during removal, but the fragments could be reconstituted to the previous shape as shown on the three-dimensional CBCT image and complete extraction could then be confirmed. The mean operating time was 30 minutes, including locoregional anesthesia.

After surgery, two (6.25 %) patients presented lingual hypoesthesia that resolved in the first three months postoperative. There were no cases of infections and no recurrent obstructive episodes. No patients experienced persistent sialadenitis after surgery.

3.3.3. Discussion

Several authors have already stated the utility of CBCT in the accurate diagnosis of sialolithiasis (Dreiseidler et al., 2010; Jadu, Lam, 2013; Van der Meij et al., 2018). We underline the additional benefit of performing this evaluation in the day of sialolithotomy with the purpose of increasing intraoperative orientation by better grasping the location of the calculus relative to the surrounding anatomical structures considered as landmarks, while minimizing the chances of calculus migration in the interval between the CBCT evaluation and the beginning of surgery.

Local anesthesia is preferred due to the smaller associated general risks, possibility to perform the procedure in an office setting and increased patient acceptability. Another advantage to the proposed technique is that the surgery and the CBCT are both performed in a seated position and therefore, there are fewer variations of the soft tissues positioning, especially in the posterior floor of the mouth.

The palpability of the calculus is considered by many surgeons one of the criteria for performing the intraoral removal (Zenk et al., 2001; Park et al., 2006; Benazzou et al., 2008). However, in the presence of a smaller calculus, or sialoliths located deep and posteriorly in the hilar area, palpation is not a very accurate indicator of the presence and location of the sialolith. CBCT allows the accurate diagnosis, but also the definition of the spatial topography of the stone in relation to the surrounding structures. This increases the surgeon's confidence in performing an intraoral approach and increases the chances of finding the sialolith in a shorter time.

Useful anatomical landmarks have been described for the detection of the hilum area during local anesthesia, in conditions of poor visualization of the surgical field and difficult access in this posterior oral region. The surgical triangle described by Park et al. (Park et al., 2013) is formed by three main anatomical structures: the lingual nerve, the medial aspect of the mandible and the posterior margin of the mylohyoid muscle. Although the surgical technique we used is not much different, the use of CBCT image analysis for the preoperative case evaluation makes the difference in allowing a preview of the patient's anatomy and the possibility to have intraoperative landmarks. It also provides the means of verifying the complete removal by comparing the number and shape of the extracted calculi. These additional findings are most important in cases of multiple lithiasis, or megaliths that are prone to fragmenting during removal. The shape of the sialolith that is viewed as a three-dimensional CBCT image helps with the reconstitution of the stone in case of fragmentation, such as demonstrated in one of the cases from our series.

One subject of debate among surgeons is the suturing of the Wharton's duct and/or the mucosa of the floor of the mouth. Combes et al. (Combes et al., 2009) suture both the canal and the overlying mucosa separately. Zenk et al. (Zenk et al., 2001) perform a new ostium by suturing the duct mucosa to the oral mucosa. Woo et al. (Woo et al., 2014) do not make a new opening for the duct but loosely suture the mucosa of the floor of the mouth over it. In our case series, we performed no suturing of the duct or of the mucosa. The wound healed by secondary intention by the help of an inserted iodoform gauze. The results were favorable, with no cases of infection or recurrent obstruction, stenosis or ranula formation. The surgery time was also shortened since the technically difficult suturing of the Wharton's duct in the proximal aspect was avoided. In their study Roh et al. (Roh et al., 2008) concluded that the performed sialodochoplasty did not have any effect on preventing the recurrence of obstructive symptoms. The only significant contributing factor they found was the complete or incomplete removal of the salivary stones. This is consistent with our results since the absence of symptom recurrence in our case series may be explained by the verified complete removal of all previously detected calculi.

Sialolithotomy and submaxilectomy are both associated with the risk of lingual nerve injury. However, during a submandibular gland removal several other nerves are also in danger of being damaged, such as the marginal mandibular branch of the facial nerve and the hypoglossal nerve (Benazzou et al., 2008; Eun et al., 2010). For this reason and supplemental cosmetic factors regarding the resulting scar and the variable depression in the submandibular region, the preservation of the submandibular gland is preferred whenever possible. Studies have shown that submandibular gland function is resumed after the removal of the sialoliths (Makdissi et al., 2004; Woo et al., 2014). Thus, sialolithotomy offers a more functional approach to managing submandibular gland calculi than does submaxilectomy and should therefore be considered as a primary procedure for the management of sialolithiasis in the presence of distal, proximal, or hilar stones.

Concluding remarks

Our study showed that gland preservation is feasible in submandibular lithiasis with good results, by performing sialolithotomy, under local anesthesia, as an office-based procedure, even in the presence of unpalpable proximal and hilar calculi. CBCT image analysis is significant for an optimal diagnosis of the location, number, and shape of the sialoliths, but particularly for an optimal understanding of the three-dimensional layout of the salivary stones. Landmarks obtained from CBCT images increase the accuracy of calculi retrieval in a short procedure.

The study described how the integration of CBCT performed in the day of surgery helped increase confidence in approaching difficult cases by intraoral route and led to the predictable removal of all detected calculi in a short surgery time.

3.4. SUSPENSION TECHNIQUES FOR FACIAL NERVE PARALYSIS FOLLOWING PAROTID GLAND SURGERY

Temporary or permanent facial palsy is a common result of nerve damage following head and neck surgical procedures, particularly after parotid gland tumor removal or skin malignancies. The postoperative facial nerve dysfunction is not only a cosmetic problem, but a functional problem as well. Depending on the location of the nerve injury at the level of the trunk or certain branches, important functions such as facial expression, eye closure, mastication, deglutition and phonation can be affected (Michaud et al., 2015).

Paralytic lagophthalmos subsequent to facial nerve damage is characterized by incomplete closure of the eyelids, malposition of the inferior eyelid, loss of blinking and prolonged corneal exposure. These modifications regarding the normal position and function of the eyelids can lead to exposure keratopathy, abrasions, ulcerations, eventually leading to infectious complications and even blindness (Joseph et al., 2016; Homer, Fay, 2018).

The maxillofacial surgeon plays an important role in the diagnosis and treatment of facial nerve palsy sequelae. The management of paralytic lagophthalmos depends on many factors such as the underlying cause, the severity of the nerve injury and of the ocular symptoms and the expected duration of the recovery (Joseph et al., 2016).

Our knowledge regarding the management of the existing functional and cosmetic impairments in facial paralysis patients was presented in the following book chapter:

- ✓ Popescu E, Ciocan- Pendefunda CC, Costan VV. Attitude toward the facial nerve in extended parotidectomy. in: Costan VV (ed) Management of Extended Parotid Tumors. Springer, 2016.

The facial appearance in facial paralysis patients, triggers thought patterns associated with negative emotions, both as self-image and as a perceived image by other people. This is due to the existing facial asymmetry with a downward orientation of the genian and perioral tissues, as well as the sagging, tired appearance of the eyes, with accentuation of the inferior orbital rim contour. The abnormal facial appearance adversely affects the social interactions of these patients (Michaud et al., 2015). The functional disturbances linked with facial paralysis are even more socially debilitating, impeding normal public outings due to unpleasant features, like saliva leakage (Coulson et al., 2004). The quality of life of these patients is significantly improved by using simple facial reanimation procedures.

Static procedures for reconstructing the paralyzed face are periodically revised and refined, in order to achieve maximum benefits, with minimum discomfort and complications. The procedures involved in static reanimation are constantly inspired and adapted from facial rejuvenation techniques that include various surgical procedures targeted at specific anatomical areas, the use of facial slings, botulinum toxin and combined techniques (Tavares et al., 2017).

In the last years, a new category of surgical threads has gained increased popularity in the area of minimally invasive face-lifts, i.e. the barbed threads. Although extensively used in plastic surgery for performing face-lifts (Tavares et al., 2017), to our knowledge, few studies (Choe et al. 2017) have been published so far regarding their effectiveness in the static rehabilitation of facial paralysis.

One of our main concerns was the continuous development of the techniques used for increasing the quality of life of facial paralysis patients. Among the contributions made was the use of cosmetic facelift dedicated barbed threads for improving facial paralysis sequelae. Our original article on this subject was one of the first to be published in the literature:

- ✓ **Costan** VV, Popescu E, Sulea D, Stratulat IS. A new indication for barbed threads: static reanimation of the paralyzed face. J Oral Maxillofac Surg 2018; 76(3):639-645.

The purpose of the study was to determine the outcomes of the minimally invasive barbed thread insertion for ameliorating the functional and aesthetic sequelae of facial paralysis patients following parotidectomy for the resection of malignant tumors, in order to refine the technique and improve future results.

3.4.1. Materials and method

We performed a retrospective study, including patients with facial nerve paralysis, that underwent closed percutaneous static facial reanimation using barbed sutures. We selected only the patients in which facial nerve paralysis was the result of parotidectomy performed for the removal of a malignant tumor, with a follow-up period of minimum one year. We analyzed the general patient information, the technique of thread insertion and the outcomes.

3.4.2. Results

- **Clinical characteristics**

A total of 18 patients were identified, 7 women and 11 men, aged between 41 and 84 years old. All patients presented with facial asymmetry. The main addressing concern was related to functional disturbances in 16 cases, and to aesthetic disturbances in two patients. All patients presented with ptosis of the oral commissure and lack of tonus in the genian region. Eight of them also had incomplete palpebral closure due to the downward pull of the ptosed genian soft tissues. Ten patients had incomplete eyelid closure due to lack of function of the orbicularis oculi in addition to the inferior pull caused by the weight of the midface soft tissues.

- **Therapeutic approach**

The criteria for performing the barbed thread insertion were the presence of facial nerve paralysis, as well as other associated factors that would contraindicate more complex methods of facial reanimation (advanced age, presence of comorbidities), or the refusal of the patients to undergo further complex open surgery or general anesthesia.

The average time between the paralysis onset and the correction procedure was between one and 19 months. Seven of the included patients had previous attempts of restoring facial symmetry by static or dynamic procedures.

Local anesthesia of deeper tissues was not needed for insertion. EMLA® cream could be used for the skin and a light sedation was commonly added by oral administration. The threads were then inserted at different depths, depending on the desired result.

For the insertion we used commercially available self-retaining monofilament polydioxanone (PDO) 2/0 double-cog threads (Prime PDO LIFTING form BS Medical®) that are commonly employed for face-lifts. The barbed thread comes inside an insertion needle and therefore the placement is simple and quick. We used threads of different lengths, according to the area of insertion and the desired effect. The needle size was 23 G in all cases, while the length was 38 mm for the frontal area, and 50, 60 or 90 mm for the cheek region. The incisionless static reanimation procedure that uses barbed threads is further described in detail.

Initially, the symmetry points of the face were evaluated, marking the approximate points of correspondence to the level of the contralateral oral commissure, the location of the nasolabial fold, the position of the maximal volume of the cheek and the maximum convexity point of the brow arch. This enabled a better planning of the desired lift. Some overcorrection was always advisable, since a small dropping of the tissues is generally noticed following the procedure.

The anchorage points were then marked at the level of the anatomical structures that we aimed lifting. We called anchorage or grasping points, those points located at the inferior end of the thread, where the lift of the tissue begins. Starting from the anchorage points in an upward direction, the weight of the lifted tissue was redistributed along the thread through the existing barbs, until reaching the superior end of the thread. For best results, anatomical landmarks were used to identify the anchorage points in the prolapsed tissues.

We preferred following the curved line of the nasolabial fold, from the superior and lateral aspect of the ala nasi towards the external aspect of the modiolus. Two to three anchorage points were needed at this level. The modiolus was a key anchorage point for achieving an appropriate lift of the lip corner. This anatomical point was found slightly lateral and up from the oral commissure. The distance could be approximated by palpating the contralateral side during function. If using one or two threads at this level, the anchorage thus obtained allowed a very efficient pull-up of the tissues, without deforming the upper lip. We generally used one thread for the modiolus, a second one slightly lateral to the previous, passed more superficially in order to create a dimple, and lastly two additional ones also passed superficially at one third and two thirds of the nasolabial fold, in order to shape it.

In patients with facial nerve paralysis, the transition from the inferior cheek region to the chin becomes apparent due to the formation of a fold induced by the ptosis of the more mobile cheek soft tissues over the more adherent chin region. This fold becomes apparent also in elderly people and is noticed as a downward line from the oral commissure towards the mandible. One or two anchorage points were also usually needed to grasp the tissues here.

The appropriate height of the brow was determined by identifying the location of the maximum convexity of the brow arch and lifting this point was performed to reach the same level as on the contralateral side. This maximum convexity is commonly located between the internal two thirds and external one third of the brow and is usually more accentuated in women. At least one additional thread was needed external from the previous one in order to achieve symmetry. The lift was designed to be smaller for the exterior thread and starting slightly more inferior following the arch. The grasping points were located inside the eyebrow.

After the marking of the grasping points, the vector lines were decided and marked. In the cheek region, most forces were directed obliquely towards the temporal area. Some vertical threads were inserted in order to support the weight of the cheek and redistribute the tissues more evenly in a net-like pattern, achieving a symmetric appearance of the maximum volume of the cheek. Progressively shorter threads or threads inserted consecutively at different levels, in a “ladder”, were needed in the cheek area for even distribution and natural results. On the forehead, the vector lines were directed vertically.

For support and adequate lift, most threads were inserted at the level of the superficial muscular aponeurotic system, since this is a fascial structure that is more reliable for anchorage and mobile in rapport with the underlying structures. When redistribution of the skin was needed in a specific area, the threads were inserted more superficially. For the specific case of the nasolabial fold, the threads were inserted to purposefully create a dimple at the exit point, in order to recreate the crease by several dimples.

The threads were passed starting at the inferior aspect and exiting at the superior one, while uplifting and supporting the tissues with the non-dominant hand, in the direction of the thread insertion. The direction was usually oblique from the nasolabial fold and from the oral commissure towards the temporal area, and vertical from the brow towards the hairline. Slight variations could be made, depending on the desired result. Additional and more vertical threads in the cheek area were used to reinforce and stabilize the oblique threads, creating a net-like pattern.

On average six to 10 threads were needed for static facial reanimation. This depended on the specifics of each case, the number of facial nerve branches involved, the constitution of the patient and his/her main complaints.

The patients had periodic follow-ups for at least one year and reinsertions were scheduled depending on the maintenance of the results, on average every six months.

- **Procedure outcomes**

Facial appearance improved in all cases to a satisfactory degree and the effect was noticeable immediately after the procedure. No important edema developed as a result and bruising was minimal. A small drop in the tissues was noticed in the first week following the procedure. However, this had been anticipated by performing overcorrection at the time of the surgery. Small adjustments were added in the early postoperative period in three cases, according to the feedback received from the patients.

Facial symmetry improved in all cases. The position of the oral commissure was corrected, the nasolabial sulcus was better defined and the tonus of the genian region increased, with resulting functional improvements regarding oral competence at rest and during function. The diction also improved due to the increased tonus of the cheek area.

Optimal results regarding the restoration of eyelid closure were achieved in eight patients with thread insertion alone. Although the position of the lower eyelid was improved after thread insertion in all patients, for 10 of them, additional procedures were necessary for further enhancing of the results regarding lagophthalmos, including a gold plate insertion in seven patients and autologous fat grafting in three cases.

The additional gold plate insertion in the upper eyelid was necessary in patients with important lagophthalmos due to orbicularis oculi disfunction and paralytic ectropion, for upgrading the result on palpebral closure, while the patients with a smaller degree of lagophthalmos caused by the mechanic ectropion due to the inferior pull of the genian soft tissues, had good outcomes with just thread suspension. In three of the patients, autologous fat transfer was performed at the level of the genian and the inferior palpebral region between consecutive thread reinsertions. After obtaining an increased support for the lower eyelid by lipofilling, subsequent thread insertions allowed further small adjustments for lagophthalmos improvement.

Subsequent thread insertions for maintaining the results were performed on average every six months. The number of threads necessary for achieving the same results at reinsertion was, at the most, half of the initial number. There were no recorded cases of infections or thread extrusion.

The results following the insertion of barbed threads (Fig. 3.4.1.) are outlined in the following two examples of cases (Fig. 3.4.2.- 3.4.8.).

Fig. 3.4.1. Barbed threads of different lengths

Fig. 3.4.2. Example 1: Patient with facial nerve paralysis after parotidectomy for a malignant tumor

Fig. 3.4.3. Example 1: Static early appearance following the insertion of barbed threads

Fig. 3.4.4. Example 1: Dynamic early postoperative appearance after barbed thread insertion

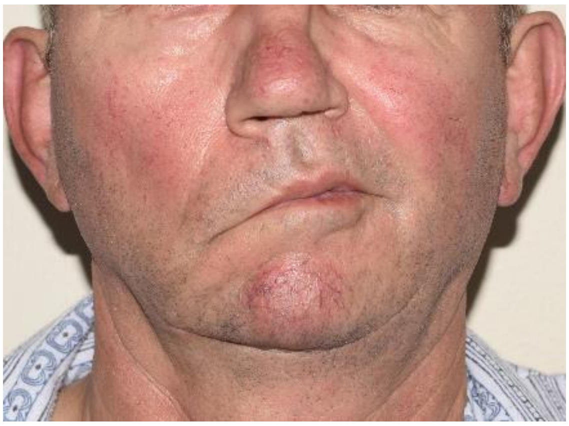

Fig. 3.4.5. Example 2: Patient with facial nerve paralysis following a malignant parotid tumor resection - preoperative static aspect

Fig. 3.4.6. Example 2: Patient with facial nerve paralysis following a malignant parotid tumor resection - preoperative dynamic aspect

Fig. 3.4.7. Example 2: Patient with facial nerve paralysis following a malignant parotid tumor resection - static aspect after barbed thread insertion

Fig. 3.4.8. Example 2: Patient with facial nerve paralysis following a malignant parotid tumor resection - dynamic aspect after barbed thread insertion

3.4.3. Discussions

Facial paralysis of any etiology can benefit from the easy insertion of barbed sutures, whenever it is established that a dynamic functional reconstruction cannot be performed safely. For example, patients undergoing resections of extended parotid malignancies can benefit mostly from simple static procedures, since the resulting defects involving several anatomical layers and the lack of local vessels and soft tissues would make a dynamic reconstruction extremely challenging (Beer et al., 2013; Le Louarn, 2015).

The advantages of barbed threads for the suspension of the paralyzed tissues in open procedures, by anchorage to the temporal fascia, have been highlighted in several publications (Citarella et al., 2008; Le Louarn, 2015). We describe a different way of addressing this issue, using commercially available barbed threads in a short percutaneous incisionless procedure. In our experience, barbed threads have proved useful in rendering static procedures even simpler and with good results when used appropriately.

Since self-retaining barbed sutures are usually indicated in performing face-lifts for mild aging (Savoia et al., 2014), it might seem that an extreme asymmetry and ptosis of the soft tissues due to seventh nerve paralysis is an unlikely indication. However, in our experience, the results are favorable, and this good outcome seems paradoxically related to the lack of facial movements.

Concerns regarding restricting facial mobility following the surgery are not an issue in the case of facial paralysis. This contributes to the good results by not modifying the initial position of the threads, which will be further reinforced by the formation of fibrous tissue around the suture (Atiyeh et al., 2010).

Additionally, a long-standing paralysis leads to muscle atrophy (Beer et al., 2013). Together with the decrease of adipose tissue occurring normally with advancing age, or the loss of soft tissues that are removed surgically, this will lead to a lack of volume and therefore decreased weight of the tissues to be suspended (Leckenby et al., 2015). A decreased weight will result in less traction along the thread and more stable results. In certain situations, when the weight of the tissue is increased due to constitutional features or the presence of a free flap reconstruction, results can be improved by increasing the number of threads used for additional support and volume distribution.

In oncologic patients with facial paralysis the main aim is to restore facial symmetry (Leckenby et al., 2015). Therefore, the amount of facial lift needed is just enough to overcome tissue ptosis without the need to address skin excess, since the aim is not to provide a younger look, but merely to achieve a symmetric appearance. In such instances, contrary to making these patients look younger, in order to achieve symmetry, we are actually trying to recreate the lines created by the old age, such is the nasolabial fold.

One important problem is caused by the reduced tonus of the cheek muscles following denervation, which leads to the “fall” of the oral commissure. The functional consequences consist in phonation disturbances, but most importantly in eating impairments, due to inefficient containment and coordination of the cheek and lip area during mastication and deglutition (Ghali et al., 2011). Consequently, drooling appears, and, between meals, the food remains in the inferior oral vestibule within the “bags” created by the decreased muscular tonus.

Reinforcing the cheek by upward traction will disband the pocket formed in the inferior vestibule and will help maintaining the tension during mastication, while lifting the corner of the mouth will impede food and saliva leakage from the oral cavity.

Lagophthalmos in facial paralysis leads to the most bothersome symptoms, that also threaten the loss of vision on the affected side. It is one of the main reasons for indicating reanimation procedures. Many static techniques have been developed to address this issue, but the outcomes are not always optimal, since it is frequently necessary to perform several types of procedures to achieve best results (Le Louarn, 2015; Sulamanidze et al., 2018). This was also true in our case series, since seven patients had an additional gold plate insertion in the superior eyelid. Still, the advantages of barbed thread insertion are that it targets two main accentuating factors for lagophthalmos- the inferior and lateral positioning, as well as the loss of tonus of the inferior eyelid, and the inferior pull on the lower eyelid from the drooping genian tissues. Bringing the bulge of the cheek to the initial position, by insertion of the barbed threads, will restore the normal contours of the region, the malar prominence and the submalar slope, but more importantly it will decrease the pull on the lower eyelid and therefore decrease the degree of ectropion (Leckenby et al., 2015). By increasing the volume of the zygomatic region, additional support is ensured for the inferior eyelid (Sulamanidze et al., 2018) and at the same time the traction on the eyelid is decreased, with positive outcomes regarding lagophthalmos. Subsequent procedures addressing this functional impairment should be evaluated after performing the midface lift. Gold plate insertion in the superior eyelid is an effective and simple operation that can be used to complete the static barbed thread reanimation procedure, as demonstrated by our experience.

In repositioning the cheek and in restoring face symmetry, the nasolabial fold needs to be addressed as a key area. Although anatomically defined as a distinct structure, the nasolabial crease is not apparent in the paralyzed face. Studies have determined the presence of muscle fibers in the structure of the crease and its surroundings, explaining the disappearance of the fold in seventh nerve paralysis (Beer et al., 2013). Since its formation is important for the function of smiling, the movement of the lip elevator muscles and the positioning of the cheek soft tissues and of the oral commissure, there is a natural need to reposition all the involved structures in order to restore the crease (Rubin et al., 1989). In the absence of facial movement, there is a supplementary need for mechanical means of redefining the fold, by using suspension threads within the crease outline. We achieved good definition of the nasolabial sulcus using barbed threads.

Following the gradual resorption of the polydioxanone (PDO) threads, taking place over a period of six to eight months, the collagen synthesis is continuously stimulated, leading to the formation of a scar tissue, that will further contribute to the retraction and maintenance of the tissues in the desired position. Studies have shown that the strength of the suture decreases, as the formation of the fibrous tissue adjacent to it advances (Atiyeh et al., 2010). Over time, the scars soften, and the effect of the threads diminishes. Therefore, there is a need for additional insertion of barbed sutures. The ease of the procedure allows this not to be a real issue, since the technique is readily reproducible any time. In anticipation of this gradual loosening, reinsertion should be scheduled and performed before there is a significant decrease of the previously obtained results.

Concluding remarks

No matter the etiology of facial paralysis (postparotidectomy, posttraumatic and following surgery for acoustic neuroma), reanimation using barbed threads offers similar results to other static reanimation techniques, with the advantage of an even simpler, incisionless procedure, that can be repeated and completed as many times necessary to refine the results, with minimal risks and in a short operating time.

The insertion can be performed under local anesthesia and in short sessions, rendering favorable, reproducible results that help the social reinsertion of patients with facial paralysis. Facial symmetry, as well as functionality regarding oral competence, diction and mastication are all improved following this technique. Lagophthalmos is improved by rendering support to the lower eyelid, as well as repositioning it, which results in an obvious amelioration of the important periocular symptoms associated with this condition. Considering the simplicity of the procedure, it can become an attainable alternative to previously used and more time-consuming open surgery static reanimation techniques.

The quality of life of facial paralysis patients is greatly improved using this simple technique that can be readily repeated any time necessary. The minimally invasive technique, the recent availability of the suspension materials, low complication rate and good overall results recommend this procedure for the static treatment of facial nerve paralysis.

SECTION II.
PLANS FOR FUTURE DEVELOPMENT REGARDING RESEARCH AND CAREER ACTIVITY

II.1. DIRECTIONS FOR FUTURE RESEARCH

In my future activity I intend to focus on the constant development of the existing research strategies, as well as expanding to new areas of research. I will continue to gradually improve my skills in the professional, academic and scientific domains and carefully balance all areas of my work. I will also persevere in developing research teams involving professionals from the same field, but also from different specialties, for engaging in common research projects. Establishing collaboration with maxillofacial departments in other universities is another desiderate for creating partnership projects and research networks. I will keep on participating with papers in national and international scientific manifestations, presenting the results of ongoing studies, as well as publishing manuscripts in ISI rated and BDI indexed journals.

Specific objectives for future development in my research career are listed below:

- Determining main directions of future research in accord to the most recent topics of interest in the field of maxillofacial surgery;
- Favoring the research directions that have the greatest chances to be transferred and applied to medical practice;
- Achieving valuable original results to be presented in national and international scientific events, as well as published in highly accessed ISI and BDI journals, or monographs;
- Identifying the modalities for participating in research grants inside multidisciplinary teams for constructing common projects with increased impact and high applicability;
- Exploring possibilities of research projects for interdisciplinary and inter-university studies centered on specific objectives;
- Participating in interdisciplinary medical studies for the advancement of current knowledge regarding diagnosis and treatment;
- Encouraging students and residents to participate in mixed research teams and harness the obtained results in scientific communications, meetings, and in the contents of bachelor’s thesis;
- Selecting the most appropriate candidates for doctorate studies that show passion about academic research and have interest in pursuing specific topics of research from the ones deemed the most suitable;
- Searching for modalities and collaborations for upgrading the existing infrastructure for research.

Some of the research subjects that I am interested in developing and represent ongoing and future studies are briefly described below.

1. Improved methods of epitheses retention for orbital and midface defects

Facial deformities following ablative surgery, trauma or congenital disorders markedly benefit from reconstruction using facial prostheses. Above all, complete or partial loss of organs like the orbit and nose are best reconstructed using epitheses, since they are most accurate in reproducing the contours and projection of the lost tissues.

Even with the constant development of microvascular free flap reconstruction techniques, facial prostheses still have an important role in covering extended defects of the midface and orbital region. Their main advantage is the possibility to directly observe changes in the residual tissues and diagnose tumor recurrences early in the evolution, which increases chances for prolonged patient survival. Furthermore, complex methods of reconstruction including free flap surgery, are not always advisable in patients with important comorbidities, due to the lengthened surgery time and the higher rate of general and local postoperative complications. Epitheses are also useful in addressing extended defects when other reconstructive methods have failed, or as a complementary method to other plasty procedures. Epitheses can also be used in association with flap reconstruction when the presence of a cerebro-spinal fluid fistula dictates the need for flap coverage and fistula closure.

Although good coverage and function are often achieved with flap reconstruction, the appearance cannot be optimally restored in one session. Several revisions are commonly necessary for achieving acceptable aesthetics. Additionally, in cases of patients with high esthetic demands, the facial prostheses offer superior results and can be used as a permanent or transitory solution, in between staged reconstruction procedures. Especially for the esthetically stringent areas, like the orbital region, only an epitheses can accurately reproduce the aspect of the eyelids and globe. The painting of the epitheses is of outmost importance in this regard due to the necessity for matching individual skin coloring, and the color of the contralateral iris, for achieving less noticeable prostheses.

Facial epitheses have the advantage of restoring an optimal facial appearance immediately postoperative, even for difficult to reconstruct regions, like the periorbital and nasal areas. This allows rapid social reintegration of the patient and reduces the psychological impact of such extensive surgery. Function is also restored due to space filling and separation of cavities. The disadvantages of epitheses are minor and can be reduced. They include the decreased adherence to the defect edges with certain retention techniques, the weight, the necessity for repeated insertion and removal, as well as the need to clean the epithesis and the sometimes-difficult insertion.

Classical methods for facial prosthesis retention imply taking advantage of anatomical countersinks and the use of tissue adhesives. Still, making the most out of the existing grooves, contours and shelves requires an experienced surgeon and a good collaboration with the technician, since multiple refinements of the epithesis are often necessary for ensuring good confinement. Three-dimensional printing techniques for epithesis construction can improve the fitting of the epithesis to the existing defect, as well as the appearance. The use of three-dimensional printing in facial prosthesis construction avoids the laborious methods of defect impression taking, implying the use of a facial mask. It is in plan to include three-dimensional printing for epitheses development as a future research direction. The purpose is evaluating the outcomes obtained by this method compared to the classical construction of facial prostheses regarding appearance and function restoration, as well as the complexity and time necessary for obtaining the epithesis.

Retention can be significantly improved by designing implant retained facial prostheses. Dental implants offer suitable alternatives to the more expensive and less available specially designed extraoral prosthetic implants. A good collaboration is needed between the maxillofacial surgeon, implant specialist, prosthodontist and technician for the planning, construction and insertion of suitable implant retained facial prostheses. The number of implants needed for achieving stability and the type of associated retention systems like bar-clips, O-rings, or magnet retention, are different according to the characteristics of each defect and the condition of the local bone and soft tissues. In extensive defects following the ablation of malignant midface tumors, enough bone for implant placement may not be available in the most favorable locations for contention. Still, suitable bone is generally found in the superior and lateral orbital rims, glabella, the anterior nasal spine region, the zygomatic arch and the zygomatic bone, for most orbital and midface defects.

As a direction for future research we aim to determine the optimal conditions for implant insertion in extended facial defects involving the orbital region and the midface region, with the purpose of improving the stability and retention of facial prostheses. Among the main concerns for future studies are the type of implant, the three-dimensional configuration in positioning the implants, the implant supported mechanical means for confinement, as well as the most suitable locations for insertion regarding the availability and quality of the existing bone and overlying soft tissues. The best timing for implant placement will also be assessed. Implant insertion can be performed during the initial tumor removal surgery. A more accurate attitude can be to insert it in a following session. A special regard can be granted to using ozone therapy to decrease the time of wound healing, while at the same time increasing the quality of the healing.

In most cases of extensive maxillofacial defects following malignant tumor removal, the implants are placed in bone that will or has already undergone radiotherapy, with unavoidable outcomes on local vascularity, osteogenic potential and ultimately on osteointegration. Multiple studies focus on the effects of ozone therapy on enhancing healing and the local vascularization of tissues, since it increases the concentration of hemoglobin and erythrocytes, activates blood circulation and stimulates the endogen antioxidant system resulting in overall improved vascularity. Another research direction is to evaluate the effects of ozone therapy on the integration of implants and in preventing early implant loss, in patients receiving implant retained prosthesis.

Furthermore, we are interested in evaluating patient acceptability and comfort with the implant retention method, since the purpose of the reconstruction is to improve the quality of life of the patient and to increase social acceptance.

2. The use of three-dimensional printing and stereolithographic models in the reconstruction of posttraumatic and postoperative defects

Advancements in three-dimensional printing and the recent increased availability of the printers, lead to the gradual inclusion of this technology in medical practice. The individualized stereolithographic models manufactured by 3D printing have multiple uses in the medical field, from surgical training, preoperative planning, creating surgical guides, to the modelling of the reconstructive material. This is a current focus of international research, but more structured information is still necessary to improve the entire process, from the software used, manipulation of the electronic file, to the printing options, the obtained model and its integration in the preoperative planning and intraoperative steps. The aim is to decrease the overall time input and complexity related to virtual information manipulation, while also increasing the rate of success for constantly obtaining accurate models and their effortless use. The final desiderate is achieving patient specific reconstruction that are precise and predictable regarding function and appearance restoration.

One direction of our current and future research is the application of three-dimensional printing in the reconstruction of posttraumatic defects, especially complex midface or panfacial trauma, where adjunctive means for control of correct reduction are indicated for achieving good outcomes, decreased surgery time and less strain for the surgical team.

The stereolithic models are obtained by the three-dimensional printing of the virtual information contained in a STL (stereolithography) file, achieved by manipulating the 3D reconstruction of the patient's CT or CBCT images. Most useful in the restoration of unilateral facial defects is mirroring of the patient's healthy side on the defect side, resulting in a model representing the ideal reconstructive result that is used for shaping the reconstruction materials, or for estimating the amount of bone graft or soft tissue needed. In fractures of the central region of the face, or bilateral fractures, the mirroring technique is not applicable, but another method of virtually separating the fractured segments and reducing them in their normal anatomical configuration can be performed for achieving the STL file that will be translated in a stereolithic model of the desired final surgical outcome. Although a time-consuming technique, the model thus obtained allows a preview of the surgical outcome and is then used for an individualized shaping of the osteosinthesis plates, greatly facilitating the operative steps.

There are few studies describing the best way to virtually reduce the fracture and the use of models in facial fracture surgery. We aim to contribute to the existing literature on the subject by developing the use of stereolithic models obtained by different methods for the treatment of complex facial fractures.

Furthermore, we aim to improve the existing methods of obtaining surgical guides and apply their use in the reconstruction of complicated facial fractures, as templates for fracture reduction. This technique can also be of real value in the reconstruction of posttraumatic sequelae for establishing the osteotomy location and the degree of correction needed.

Another focus is the implementation of three-dimensional printing for the restoration of defects following the removal of benign and malignant tumors. Preoperative modelling of the reconstruction material, particularly titanium plates, titanium mesh, allows the use of less extensive incisions for access and insertion, decreased surgery time, but most importantly, it allows an individualized reconstruction that results in an accurate restoration of the facial contours at the same time with optimal functionality.

The value of this technique is best outlined in reconstructive surgery following benign tumor removal. A more precise restoration of facial symmetry is desirable in such patients, as well as optimal functional resumption. Estimating the amount of tissue needed for bone graft or flap reconstruction is best achieved using mirroring of the contralateral side and printing of stereolithic models for assessing of the final result. Likewise, modelling of the reconstructive material is best performed outside the operating room, using the constructed individualized stereolithic models. Preoperative modelling of the material is easier to perform than intraoperative, mostly due to the difficult estimation of the anatomy to be reconstructed during surgery, in a limited space, with decreased visibility and difficulty in assessing the accuracy of the modelling due to subjective quantification of the symmetry achieved, as well as the contribution of soft tissue thickness to the final result. In addition, the manipulation of the material in the wet surgical environment is more challenging and time consuming than the preoperative shaping using stereolithic models.

Surgical guides can also be constructed by three-dimensional printing to aid in composite free flap surgery involving bone reconstruction. Particularly for the fibula flap, the stereolithic model allows planning of the desired shape of the reconstructed surface and preplanning of the osteotomy sites that are registered and transferred intraoperatively using cutting guides. This greatly simplifies the duration of the surgery, decreases the complexity, ensures an individualized reconstruction and increases the predictability of the postoperative results.

3. The outcomes of structural fat grafting on chronic postoperative pain

Autologous fat transfer has many applications in maxillofacial surgery, including the filling of posttraumatic, postablation and congenital volumetric defects, as well as improving the quality of the tissues, but also the texture, mobility and appearance of scar tissue. It is a simple, minimally invasive and generally safe procedure, that can be performed under local anesthesia with sedation. There is abundant fat tissue that can be harvested from several body regions. The procedure can be repeated several times to achieve the desired results, when indicated. Its value in shaping soft tissue contours, filling spaces and restoring facial symmetry is well-known, but the effects rendered by the presence of adipose derived stem cells are the continuous focus of research, in an attempt to expand the uses of lipofilling to enhancing tissue regeneration. Epithelial hyperplasia and angiogenesis are stimulated in the presence of adipose derived stem cells. Growth factors are believed to be responsible for these effects, as well as an anti-inflammatory effect. They additionally enhance nerve repair and release by scar tissue release, increased hydration and vascularization.

Chronic pain associated with neurologic conditions, such as postherpetic neuralgia, or to the presence of posttraumatic injury, postoperative or burn scar tissue, has a debilitating effect on the patient's everyday activities and general comfort. Autologous fat transfer could have an indication for all the described conditions, with the purpose of decreasing persistent pain and increasing life quality.

Current studies on structural fat grafting seeks to establish the role of lipostructure in ameliorating scar tissue related pain, in the presence of posttraumatic, postoperative or burn related tissue scarring. This positive side effect is attributed to the release of scar contracture and nerve entrapment, but also to the anti-inflammatory effect determined by the presence of adipose derived stem cells.

We frequently perform lipofilling for restoring volume and facial symmetry, improving the texture and appearance of scars, as well as improving the sequelae of trauma or facial nerve paralysis. We aim to complete our previous studies on free fat transfer outcomes, by evaluating the degree of decrease in local pain for patients with previous surgery in the injected region. This can eventually serve in extending the indication for performing lipostructure even in patients that do not necessitate a volumetric correction in the involved area but complain of longstanding local pain.

Persistent pain has been often reported in relation to oncologic surgery and tissues exposed to radiotherapy. A particular group of interest is represented by oral cancer patients with previous tumor resection surgery, reconstruction and neck dissection, followed by radiotherapy. The procedure of neck dissection often involves dissection and trauma to multiple nerves in the neck that are then embedded in scar tissue that will be further accentuated by postoperative radiotherapy. This frequently results in tissue retraction, appearance changes, but also an increase occurrence of chronic neck pain. The additional benefit of fat grafting in decreasing local pain would allow an important increase in life quality for a great number of head and neck cancer patients with previous radiotherapy and chronic pain.

4. Increasing the success rate of microvascular free flap reconstructions in the head and neck region

Advancements in the field of reconstructive microsurgery include the raising of more complex composite flaps, as well as development of perforator flaps alongside the technique of flap raising and monitoring. The mastery of microsurgical techniques and raising of multiple types of flaps, offers great freedom in approaching difficult cases, requiring extensive reconstruction, but also delicate cases, where the aesthetic and functional demands are high. Due to the complexity of the entire procedure and all the resources involved, the development of refinements in all aspects of surgery, from indication and technique to postoperative care and follow-up, are still necessary for decreasing the chances of flap failure.

Microvascular free flap surgery implies a well-prepared operating team, advanced surgical skills, longer operating time and therefore an increased anesthetic risk for the patient. It also implies higher overall costs than most maxillofacial procedures. Still, success is not guaranteed in all cases, especially when the receiving area was previously irradiated, or the patient has multiple comorbidities influencing vascular condition.

The vessel dissection technique, tissue handling, and microvascular suture quality may contribute to some degree to the final result, but anticoagulation and flap surveillance in the postoperative time, for prompt intervention in case of compromised vascular flow, are of outmost importance in increasing the success rate. Many authors constantly perform studies in search of factors influencing flap survival and successful surgical outcomes. We aim to analyze our existing experience on microvascular free flap harvesting technique, flap design, type of vascular anastomosis and the occurrence of postoperative complications, including flap loss. The purpose is to improve the existing protocols for increasing the chances of flap survival, as well as the reconstructive results. We also aim to quantify the importance of educating the caring personnel in intensive care on recognizing early signs of anastomosis inefficiency, as well as evaluating and improving additional existing technological means of flap vascularization follow-up.

Another research direction is the introduction of new types of free flaps in clinical practice, as well as refining the techniques for the already long-time used flaps, in terms of flap design and dimensions, composite flaps. The purpose is to decrease the need for multiple staged revision surgeries following the reconstruction of important facial deformities by proper planning of the amount and type of tissues needed, as well as purposefully designing a shape for the harvested flap in order to better follow facial units and improve reconstructive results. For optimal outcomes regarding the shape of the reconstructed region, both the bone contours and the soft tissues need to be restored. Provided that, composite flaps containing bone reduce the need for a secondary surgery to recreate the support frame for the soft tissues. As an alternative, titanium mesh can be used in association with soft tissue flaps.

An area of future improvement is enhancing the harvesting, modelling and insetting of free flaps containing bone. In this regard we aim to use three-dimensional printing for manufacturing surgical guides and templates used in performing guided osteotomies and modelling of the harvested bone. In this manner, with proper planning and technique, the anatomy of the region ca be reconstructed with more accuracy. Multiple osteotomies, double barrel flaps, or the simultaneous insertion of dental implants for the future prosthetic rehabilitation, would allow overall improved and predictable reconstructions for oncologic patients. A more precise defect restoration can be thus obtained, in a shorter time, with enhanced functional and esthetic outcomes.

II.2. DIRECTIONS FOR FUTURE TEACHING ACTIVITY

II.2.1. Academic activities regarding students

Teaching activities plays an important role in teaching activity of any university professor. Our main role is to teach the students but is of paramount importance is how we can do this. At proper age, they are avid of information and full of enthusiasm to achieve all new competences and skilling possible. It is up to us to direct this focus not only to oral and maxillo-facial surgery.

At the same time, it is possible to select since from this stage of evolution future researcher or at least the best future residents capable to have an excellent clinical evolution.

An important argument to an easiness of relationship with students are the 42 bachelor's thesis made under my supervision. Only three years after my debut in University career I supervised such a thesis, under the coordination of my mentor Prof. Dr. Dan Gogalniceanu. Not only the number of thesis is significant but also important is the fact that students belong to Dental or Medical studies and from Dental Technique College. The level and quality of knowledge was quite different, and also different was the background for writing a scientific report, with a special appreciation for the French section students. This intense collaboration permits a good understanding of the aspiration toward possibilities and gives me the possibility to improve the didactic materials used in teaching process.

According to the possibility to develop scientific activities together with the student, I started as student with papers presented at 2 international student congresses and at 3 local scientific manifestations.

During my academic career, I supervised 12 scientific works to be presented at different national student scientific manifestations, 2 of them gaining first and respectively second prize.

Another possibility to help the development of scientific student activity was through coordination of 2 workshops.

All these activities made me acquire a good experience in working with students, with a better understanding of their actual perspective and their real necessities. This way, I acquired a good basis to develop and improve my academic activities with students. In this purpose, as future directions it is necessary to:

- Continue to update the content of course presentations in order to enhance the learning process and inspire the attention and interest of students, by performing the following:
    - ✓ Adding newly emerged information with focus on practical aspects;
    - ✓ Increasing the use of interactive methods of presentation and enhancing course delivery and design;
    - ✓ Presenting eloquent teaching materials from clinical practice, according to the curriculum and in conformity with the requirements for personal data protection, by archiving the clinical data of patients that have been diagnosed and treated in the Oral and Maxillofacial clinic, with focus on etiology and treatment;
- Constantly updating the student evaluation system;
- Developing interesting bachelor's thesis topics to inspire the interest of students in Oral and Maxillofacial Surgery;
- Selecting the most capable students with interest in research activities for participation in research studies and taking part in research teams;
- Organizing student scientific circles in order to stimulate their interest in scientific research and in the surgical disciplines;
- Encouraging and guiding the active participation of students in scientific events, as well as application for scholarships;
- Encouraging the initiatives of students to approach specific research topics from the domain of Oral and Maxillofacial Surgery;
- Organizing workshops and symposiums adapted to the student's area of interest;
- Proposing optional courses in accord with the existing demands;
- Diversifying the on-line learning environment by introducing video materials, attractive course presentations, interactive roles and online evaluation formats, in order to perform enhanced and diverse study and evaluation activities in any context requiring online learning;
- Increasing the quality of the teaching process within the discipline and in the academic field by utilizing the e-learning platform;
- Encouraging academic partnership by identifying and solving the difficulties and expectations of students in order to ensure a fluent learning process;
- Encouraging individual study and dialogue with each student;
- Development of the formative aspect of teaching, as well as the informative one, with the purpose of preparing future specialists for entering the work field and designing a successful career.

II.2.2. Academic activities regarding residents

Residents plays an important role in our teaching activity. In contrast to the students, they are already choosing the profession. In this reason, they are more focused in specific topics and the interests in what we must teach.

The teaching process has a dual role: to put a solid base of medical knowledge and to develop the necessary skills to treat the oral and maxillofacial surgical patients. At the same time, it is necessary to train the residents in such a fashion that, by using the medical knowledge, to choose the most appropriate medical solution for the patients, not only the surgical one.

Residents keep some of the social and behavioral characteristic of the students. However, there are also some important differences. A close working relationship with them gives a better understanding of their professional necessities.

I think a good collaboration with young trainees permits not only to teach them but also to easily introduce the new technologies in our activity. The most enthusiastic of them, can be ideal candidates for doctoral students. To the present day, I encouraged many residents that have shown interest in actively participating in scientific events, resulting in 24 oral and poster presentations with their important contribution. At the same time, there are 17 publications with residents in the author list.

Maybe their conceptual role was not the most significant, but participating in all the process of making the scientific work, from collecting the data on the patients to taking photos and to noting all the significant facts for research gave them a realistic view about what research means. Together with the honor to be in the collective of authors, they were stimulated to be more accurate in the medical training activity. A better understanding of the evolution of the disease under different surgical approaches permits a better choice of treatment solution.

Lastly but not the least, this attitude selects some of the residents to choose the mixture between medicine and science and to apply for a position of doctoral student.

Corresponding to the academic activities regarding resident doctors, the following are the main future development directions:

- Enhancing the training of resident doctors by teaching up-to-date, applicable medical content using updated course materials;
- Organizing clinical presentations and presentations of research in the existing literature on specific designated topics, with the participation of residents, specialists and primary physicians in order to stimulate debate and discussion;
- Encourage the active implication of residents in the learning process with accent on supervised practical activities, in accord to the resident log book;
- Teach the importance of participating in multidisciplinary teams in approaching complex cases and organize sessions of case presentation with multidisciplinary participation;
- Implementing a rigorous knowledge evaluation system regarding theoretic and practical abilities;
- Encouraging and guiding the active participation of residents in research projects, national and international scientific events, as well as application for scholarships;
- Encourage learning by experience exchange in national and international centers.

II.2.3. Academic activities regarding doctoral students

The doctoral students are the highest category of students. I believe that I must have a special focus toward their activity. In our days, the coordination of the doctoral studies involves an important responsibility. At the same time, a good choosing of this student's type can be a source of great satisfaction.

Youngness with its specific freshness and curiosity can direct our novel direction of activity to surprising technological solutions. For doctorands, can be easier than for me to understand the advantages of the last technological progresses and to apply it to my classical approach of variate medical problems.

I had the privilege to work in the same department with Prof. Dr. Eugenia Popescu. It is quite difficult to work in another way than in teams to acquire good medical, scientific, and technological results. In this direction, at least 11 ISI and 16 BDI articles have as a main author one of her doctoral students, as well as at least 27 oral or poster presentations at different national or international scientific manifestations. These intense activities, accommodated me with doctoral scientific activity and gave me the belief that I will be able to coordinate myself the doctoral students.

Corresponding to the academic activities regarding doctoral students, the following are the main future development directions:

- Selecting the most capable students and resident doctors showing interest in learning and performing scientific research, for undergoing doctoral studies;
- Establish specific areas of recent interest and development in the field of Oral and Maxillofacial surgery that would suitable for doctoral studies, in relation to the existing and ongoing research subjects;
- Teach doctorate students the newest information regarding the research topic and the practical means of achieving specific objectives, as a result of academic and clinical experience;
- Encourage doctorate students to participate in multidisciplinary teams in order to broaden the specter of ideas and find new technological solutions;
- Follow opportunities of interdisciplinary and inter-university collaborations in order to facilitate access to information, technology and experience exchange.

II.3. DIRECTIONS FOR FUTURE PROFFESIONAL ACTIVITY

I had the chance to discover, since I was student, the surgery that I liked. My mentor at that time, Prof. Dr. Stefan Luchian, not only did he open my eyes to reconstructive surgery, but also to scientific research. My bachelor thesis for medical degree consisted in an experimental study on some novel (at that time) flaps on rat. My further professional evolution was a classical one, consisting in a step-by-step evolution both for academic and medical career.

This kind of evolution is an important strong point for me that creates the premises for a foreseeable but good progress in profession. The acquired experience gives me the possibility to coordinate the collective and terms such that can have the possibility to manage effectively the challenges that may arise.

The directions of future development in my professional career include the following:

- Increasing the quality of the medical care by including improved protocols and the use of new technology:
    - ✓ Including in current practice the use of newly emerging computer planning technologies, using 3D printing and stereolithic models for decreasing the duration of surgical procedures and increasing the precision of the actual surgery and thus improving results;
- Approaching new surgical techniques in accord with the existing pathology in the Oral and Maxillofacial Clinic;
- Encouraging interdisciplinary collaborations for the management of complex case.

SECTION III.
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