SAPIENZA
UNIVERSITÀ DI ROMA

DIPARTIMENTO DI NEUROSCIENZE UMANE

DOTTORATO DI RICERCA IN NEUROSCIENZE CLINICO SPERIMENTALI E PSICHIATRIA

XXXIV CICLO

LESS INVASIVE MANAGEMENT IN NEUROSURGICAL DISEASES. MULTIDISCIPLINARY APPROACH AND LONG-TERM FOLLOW-UP

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ANNO ACCADEMICO 2018-2019

To my Family
in gratitude for their love and support over many years.

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PREFACE

The following project is comprised of five main chapters.

The first chapter describes general information about my personal PhD career, introducing the concept of a minimally invasive approach applied to degenerative diseases and deformity of the spine and to the surgical removal of intramedullary spinal cord tumors. The original article included in this chapter was performed during my PhD, because spinal surgery has accompanied my entire career as neurosurgeon since my residency program.

The second chapter introduces the concept of minimally invasive approaches to the skull base diseases in neurosurgery. This chapter describes the objective of this study: the role of stereotactic radiosurgery to treat complex neurosurgical disease of the skull. The published research on this topic, developed during my PhD program, has been included in this chapter accordingly.

The third chapter provides the topic of this study: the role of Gamma Knife radiosurgery as a minimally invasive procedure in the management of vestibular schwannomas. Chapter three describes general information about vestibular schwannomas and Gamma Knife stereotactic radiosurgery. Then, written as the primary research article, the long-term audiological follow-up after vestibular schwannomas Gamma Knife stereotactic radiosurgery is included. The idea of this study was born from the collaboration between neurosurgeons, otolaryngologists and audiologists.

I was responsible for designing the study, obtaining ethics approval, recruiting, and running participants, data collection and analysis as well as writing the manuscript. No sponsor was involved to finance the study. I was responsible for all aspects of the studies and the coauthors were given authorship for helping with data collection or analysis. Professor Mancini coordinated the research and supervised the writing of the manuscripts prior to submission.

Chapter four was written as a primary research article as well. The original article was developed with the aim of underlining the role of hearing rehabilitation with a cochlear implant in vestibular schwannoma after Gamma Knife stereotactic radiosurgery. The original article has been published as a literature review in the Neurosurgical Review journal. In the last chapter I have included some original articles published and developed during my PhD studies.

ACKNOWLEDGEMENTS

I would like to thank my mentors and collaborators for providing me with key data and information, and for making this project possible.

First of all, I would like to acknowledge my supervisor, Professor Patrizia Mancini, for giving me the opportunity to carry out this PhD program, which was very important to me. Prof. Mancini's supervisory style is the perfect balance between guidance and independence, which fosters a scientific mind ready for any challenge.

Dr Bassani, my chief, and my mentor has been very supportive and encouraging throughout this research process. He taught me the importance of a minimally invasive approach to pathologies, especially in the field of spine surgery. Dr Bassani shared with me professional knowledge that I did not know before starting this project.

I wish to express my deepest gratitude to Professor Pietro Mortini, Chief of the Department of Neurosurgery and Radiosurgery Units San Raffaele University Health Institute, Vita Salute San Raffaele University in Milan. I obtained my residency in neurosurgery with Prof. Mortini and he has followed and supported me ever since, giving me the opportunity to carry out further academic studies. His support and teachings gifted me with the perspective and direction to carry out this project.

I would like to give a big thank you to Professor Mortini's assistant, Laura Sincinelli, who is very smart, funny and always cheerful. She helped me with the hard task of getting the ethics committee approval.

I would also like to acknowledge the numerous colleagues and friends from the Department of Neurosurgery and Radiosurgery Units San Raffaele University Health Institute which help me during data collection.

I would also like to acknowledge the help of Doctors Roberto Teggi, Chiara Canova and Lucia Ornella Piccioni from the Department of Ear, Nose and Throat, of San Raffaele University Hospital, and Ilaria Giallini form Sapienza University of Rome, whose help early on with the data collection for the study made me focus on getting it right.

I would like to thank Professor Marco Artico from the Department of Sense Organs, Sapienza University of Rome, for his unwavering support, insightful comments, and helpful ideas throughout my doctoral studies.

I would like also thank my husband Riccardo for putting up with me and my professional and academic commitments. Only he knows how much work has gone into this.

Finally, I would like to dedicate this work to my late father and mother, who always desired this for me and through their tireless work ethic undoubtedly shaped me into the woman and doctor I am today.

CHAPTER 1

1.1 Intoduction to minimally invasive approach in neurosurgery

In recent years, the term "minimally invasive" has received great attention in several surgical fields, especially to promote the resolution of the many complex and vexing problems posed by the management of neurosurgical diseases.

The advent of new imaging and surgical technologies have helped to revolutionize the field of neurosurgery to ensure improved postoperative outcomes and patient satisfaction.

Unfortunately, less, or minimally invasive are not synonymous with absence of complications or drawbacks. Therefore, the goal of the modern approach to complex diseases is aimed to choose the less invasive treatment providing solutions for the drawbacks with quality of care over time.

The term minimally invasive can be intended as a treatment approach with minimal tissue invasion: smaller incisions, less blood loss, quicker return to daily activities, and increased visualization.

The present chapter describes several research projects related to the knowledge of minimally invasive surgical concepts applied to the degenerative and tumoral disease the spine.

Among the minimally invasive approach to the lumbar spine for degenerative disc disease, the first study analyzes perioperative, functional and radiological data between two techniques: anterior versus posterior lumbar interbody fusion.

The results of this study showed that anterior approaches of the lumbar spine presented earlier clinical benefit (faster return to work), lower blood loss, shorter surgical time and powerful intervertebral disc distraction with significant better segmental lordosis restoration if compared to posterior approaches.

The advantage of using the anterior technique is the possibility to achieve a complete anterior discectomy, under direct vision, after the resection of the anterior longitudinal ligament (ALL) and the insertion of large and lordotic cages. This approach, using modern minimally invasive techniques, allows for an optimal local lordosis restoration and an indirect foraminal decompression, an early perioperative pain reduction preserving the integrity of the posterior tension band. It is a muscle sparing technique, avoiding posterior muscle detachment and denervation.

The second study focused on the surgical results of the anterior approach to the lumbar spine on 269 patients. In this study perioperative results of single and multilevel anterior interbody fusion were presented. In this research the use of an endoscopic camera was emphasized to assist the mini-open retroperitoneal anterior approach.

The differences between standard mini open anterior interbody fusion and the video assisted technique mainly consisted of the use of a 30° endoscope during the dissection, discectomy and cage implantation phases.

Compared with other mini-open techniques, the video assistance allows a greater magnification and brightness of the surgical field, therefore can be considered a minimally invasive procedure.

A deep light source and a magnification on the screen allow the complete visualization of the procedure for all the surgical team. The 30° angulated camera allows a better view during dissection in the single and multilevel approach and especially during the discectomy phase. According to our results this technique potentially reduces perioperative morbidity, length of surgery and hospitalization as well as surgical approach-related complications.

The knowledge of current concepts of spinal sagittal balance has shown the restoration of the correct spinopelvic angle and especially the lumbar lordosis in L5-S1 is important to improve surgical outcomes in patients with degenerative disc disease and low back pain or spinal deformity. The cages usually implanted in anterior interbody fusion approach traditionally have a certain degree of lordosis, between 8 and 12 degrees. In recent years the use of hyperlordotic cages has been described, ranging up to 30 degrees of lordosis. The third part of the research describes the use of the new introduced hyper-lordotic cage to improve segmental lordosis restoration with the anterior retroperitoneal approach to the lumbar spine. The study focused on the segmental change in lumbar lordosis in L5-S1 disc in patients with degenerative disc disease and low back pain who underwent fusion with hyperlordotic anterior cages. The result of this study demonstrates a higher power of L5-S1 segmental lordosis restoration if compared to the older interbody implants, strengthening the advantages of this technique.

In the fourth article "New trends in spinal surgery: less invasive anatomical approach to the spine. The advantages of the anterior approach in lumbar spinal fusion" the evolution of the anterior approach and its role for all orthopedic spine surgeons or neurosurgeons has been summarized.

In this study the development of minimally invasive techniques was underlined, leading to a progressively less invasive anatomical exposure of the spine over the years.

Due to drawbacks and high surgical morbidity of open transperitoneal approaches (large skin incision, abdominal muscles trauma and major risk of retrograde ejaculation in male for L5-S1 dissection), after a transitory skepticism concerning anterior approach, less invasive routes were explored such as laparoscopic techniques and mini-open retroperitoneal techniques. Parallel to the development of less invasive anterior lumbar

exposures, was less invasive skin incisions described for single or multilevel procedures. The classical median or paramedian or S-shaped large skin incision, which extended from the symphysis to the umbilicus used in the transperitoneal approach, was progressively abandoned. In the modern era, a less than 5 cm Pfannestiel skin incision is used to expose the space L5-S1. Recently, the "keyhole" perinavel skin incision was developed for a minimally invasive exposure of both single (i.e. L5-S1 or L4-L5 or L3-L4) and multiple levels (from L2-L4 to L5-S1), all in the retroperitoneal space.

In my neurosurgical practice the expertise of anterior approaches to the lumbar spine was important to improve my knowledges in minimally invasive approaches in the management of degenerative or deformity diseases, tumors, infections, traumas and as a salvage procedure after posterior surgery.

As a neurosurgeon the knowledge of spinal surgery concepts is important to ensure the success of surgical procedures. Microscope magnification, navigation, robots and intraoperative electrophysiological neuromonitoring have also improved surgical outcomes.

In intramedullary spinal cord surgery, the combined use of somatosensorial (SEP) and motor evoked potential (MEP) is mandatory even if not always predictive of surgical outcome (false positive). The introduction of trans cranial electrical stimulation and epidural (D-wave) recordings change the predictive role of intraoperative neuromonitoring. The D-wave (epidural MEP), began the major outcome predictor in spinal cord surgery and even though muscles MEPs are lost, there may be a transient deficit but no permanent postoperative deficit if the D-wave is preserved.

Notwithstanding the advances in surgical technique and application of new technology, the management of intramedullary spinal cord tumors remains challenging and can be associated with a not negligible neurologic morbidity that may dramatically worsen patients' quality of life. As it was one of the most important topics of my study program the last piece of research focused on surgical and radiologic prognostic factors in intramedullary spinal cord lesions. The study aimed to perform a comprehensive data analysis of 47 consecutive patients treated in 8 years and to observe how clinical, radiologic, and surgical factors affect early and long-term outcomes, recurrence rate, and survival. According to our analyses, better chances of recovery and a good postoperative outcome were observed in younger patients with better preoperative functional status. It also found surfacing lesions had a better early functional outcome than did intramedullary located lesions. Surgery should probably be performed before patients' neurologic decline, aiming to achieve maximal resection without compromising patients' quality of life.

1.2 Functional and radiological outcome of anterior retroperitoneal versus posterior transforaminal interbody fusion in the management of single level lumbar degenerative disease

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Original Article
Neurosurg Focus. 2020 Sep;49(3):E2

Keywords: Anterior Lumbar Interbody Fusion, Transforaminal Lumbar Interbody Fusion, degenerative disc disease, radiological outcome, functional outcome, Lumbar Lordosis

Abstract

Introduction

In the present study we compare Anterior Lumbar Interbody Fusion (ALIF) and Transforaminal Lumbar Interbody Fusion (TLIF) technique in a homogeneous group of patients affected by pure single level L5-S1 degenerative disc disease (DDD) and Post Discectomy Syndrome (PDS). The purpose of the study was to analyze perioperative, functional and radiological data between the two techniques.

Materials and methods

A retrospective analysis of patient data was performed between 2015 and 2018. Patients were clustered in 2 homogeneous groups (Group 1: ALIF, Group 2: TLIF) according to surgical procedure. A statistical analysis of clinical perioperative and radiological findings was performed to compare the two groups. A musculoskeletal radiologist retrospectively revised radiological image.

Results

Seventy-two patients were comparable in terms of demographics features and surgical diagnosis and included in the study: thirty-two (44.4%) male and 40 (55.6%) female with an average age 47.7 years. Mean follow-up was 49,7 months. Thirty-six patients (50%) were clustered in Group 1 and 36 (50%) in Group 2. Preoperative diagnosis was DDD in 58 patients (80.5%) and post discectomy failure in 14 patients (19.5%). We observed significant reduction of the surgical time (107.4 minutes *vs* 181.1 minutes) and blood loss (188.9 *vs* 387.1 ml) in Group 1 (P<.0001). No significant difference in complications and reoperation rate between the two groups (P=0.561) was observed. Significant improvement of functional outcome was observed in both groups (P<0.001) without significant difference between the two groups at the last follow-up. In Group 1 a faster median time of return to work (2.4 months vs 3.2 months) was recorded. Significant improvement in L5-S1 postoperative lordosis restoration was register in ALIF Group (-9.0 vs-5.0 P=0.023).

Conclusions

According to our results, interbody fusion is effective in discogenic pain surgical management. Even if clinical benefits were achieved earlier in the ALIF group (better scores and faster return to work), both procedures improved functional outcomes at last follow-up. ALIF group showed significant reduction of blood loss, shorter surgical time and better segmental lordosis restoration if compared to TLIF group. No significant differences in postoperative complications were observed between the groups. Based on our results, ALIF technique enhances radiological outcome improving spinopelvic parameters, when compared to TLIF in the management of adult patient with L5-S1 DDD

Introduction

In adult patients affected by degenerative disc disease (DDD), with chronic low back pain, interbody fusion is performed to achieve pain relief with the aim of obtaining first a solid bony fusion and secondly the restoration of the segmental lordosis according to the Pelvic incidence. Different techniques, posterior, anterior, lateral, combined, have been developed and advantages or drawbacks widely investigated [1-8]. The advantages of ALIF technique are the possibility to achieve a complete anterior discectomy, under direct vision, after the resection of the anterior longitudinal ligament (ALL) and the insertion of large and lordotic cages. This approach, using modern minimally invasive techniques, allows for an optimal local lordosis restoration and an indirect foraminal decompression, an early perioperative pain reduction preserving the integrity of the posterior tension band [1-9]. ALIF approach-related complications rate accounting between 8.4 to 31.1% in the large series [2-3]. The most important complications are vascular injuries, especially venous, accounting between 1.9 and 24%, mostly at L4-L5 space (iliolumbar vein) [4-5]. Visceral injuries are uncommon. Neural structures injuries can include sympathetic dysfunction, and retrograde ejaculation in male (3-5% of men cases) [5-6]. Among posterior approaches, the advantages of TLIF include the unilateral access to the disc, eventually direct monolateral decompression reducing perineural scarring tissue and the possibility to perform both interbody and posterolateral fusion. TLIF approach-related complications are dural tears and root injury, poor discectomy and end plate preparation, screws and cage malpositioning or migration [7-8]. According to the literature, the perioperative TLIF complications rate account between 14.2% and 25.4% in the large series [7-8]. Rate of dural tears range between 0 and 20%, root injuries occur in 1-3% of cases, symptomatic screws misplacement occurs in 4-9% of cases and cage migration is an uncommon but potentially serious complication [8]. Many comparative studies report the same fusion rate between these different techniques and better radiological results in term of segmental lordosis for ALIF [10]. However, comparative data on surgical results and functional outcome of each procedure are unconvincing probably because heterogeneous sample are analysed resulting in limited statistical power [2,10]. The purpose of this study was to compare retrospectively the two techniques (ALIF vs TLIF) in two homogeneous groups of patients in term of numbers, gender and age affected by pure single level L5-S1 DDD and post discectomy syndrome (PDS). An analysis of perioperative, functional and radiological data between the two techniques was done.

Materials and methods

This is a retrospective analysis from the review of the 2° Spine Surgery Unit of IRCCS Galeazzi Hospital database between 2015 and 2018 with minimum 2 years follow up (mean follow-up: 49,7 months). Clinical and Radiological de-identified registries were used to track patients care and outcome without a direct patient involvement even if informed consent was obtained. Patients ≥18 years old, with single level L5-S1 interbody fusion performed by ALIF and TLIF techniques for DDD or PDS were selected and included. TLIF technique was performed in case of DDD or PDS associated to bony stenosis and ALIF technique in pure DDD or PDS or with association of soft stenosis (indirect decompression). Only patients with complete information in the database at the last follow-up were considered for the study. Patients with significant comorbidities (diabetes, inflammatory diseases, Body Max Index ≥30), post traumatic deformity, infections, spondylolisthesis or previously fused, were excluded. Surgery was performed in order to achieve pain improvement and to prevent neurological worsening. A single senior spinal surgeon trained in anterior approaches (R.B) treated all included patients clustered into Anterior (Group 1) and Posterior (Group 2) groups. Clinical, radiological and surgical data of each patient were collected until final follow up. Clinical and functional outcomes were assessed by visual analogue scale (VAS) for back pain and leg pain and Oswestry Disability Index (ODI) scoring systems. A Spine registry (The IOG Spine-Reg) was used to track clinical follow-up. Radiological follow-up was obtained on 2nd day post op, after 3 months, and then every 12 months for 2 years. All Radiological data were obtained by direct measurement of biplanar Full Spine X-Rays on EOS^{R} imaging platforms and collected in the Institutional Radiological registry. Each image was imported in Sectra Workstation IDS7 and elaborated with Ortho Toolbox **(Figure 1)**. Lateral and coronal images were considered: preoperative and postoperative spinopelvic parameters were assessed and compared. Fusion at the last follow-up was retrospectively assessed by a musculoskeletal radiologist with 15 years' experience in musculoskeletal imaging (LMS) on both Computed tomography (CT) scan and X-rays, which, especially in the presence of tantalum cages, could be less subject to artefacts. Brantigan interbody fusion grading system was used to define radiological evidence of fusion on CT scan [11]. Grade 4 and 5 was considered as fusion. The presence of bone bridging in the disc space or in the anterior part of the disc space on X-rays was also used to confirm fusion.

Statistical Analysis

Statistical analyses were performed using Graphpad Prism v5.0 (GraphPad Software Inc., La Jolla, CA, USA). Data were expressed as median and interquartile range (IQR) or mean and standard deviation (SD) as specified in each case. Normal distribution of all variables

was tested using Shapiro-Wilk test. One-way ANOVA and Kruskal-Wallis test with Dunn's post-test were applied to assess differences among different groups and time points, in case of normal and non-normal data distribution, respectively. Similarly Student t test or Mann-Whitney tests were used for the comparisons between two groups. P values <0.05 were considered statistically significant.

Results

Population

The analysis of our database showed 153 patients that underwent surgery for single level L5-S1 degenerative disease treated with ALIF and TLIF techniques. Out of these 153 patients, 56 (36.6%) were excluded due to exclusions criteria and 25 (16.3%) for incomplete data at the last follow-up. All the 72 included patients were comparable in terms of demographics features and diagnosis. Thirty-two patients were male and 40 female, average age was 47.7 years (Range 28-83; SD 11.5); median age was 46 years. Mean follow-up duration was 49,7 months (Range 12-108 months; SD 27.6). Thirty-six patients (50%) were clustered in the Group 1 (12 male, 24 female, average age was 46.09,SD 9.154). Thirty-six patients (50%) were clustered in the Group 2 (16 male, 20 female, average age was 50.55, SD 13.41). Preoperative diagnosis was DDD in 58 patients (80.5%) and PDS in 14 (19.5%). Thirty-one patients with DDD in Group 1 (86%), and 28 patients with DDD in Group 2 (78%). Five patients with PDS in Group 1 (14%) and 8 PDS in Group 2 (22%).

Preoperative Spino-Pelvic parameters

In Group 1, mean PI: 49.4 (median value 46°, SD 11), PT: 16.8 (median value 17, SD 7.3), SS was 31.1 (median value 33, SD 8.3). The mean LL in L1-S1 was 48.7 (median value -49, SD 11). Lower Lumbar Lordosis L4-S1 (LLL): 31.5 (median value 31.7, SD 7.5) and L5-S1 Lordosis: 17 (median value 16.5, SD 6.2).

In Group 2, mean PI: 50.9 (median value 49, SD 9.7), PT: 17.2 (median value 16, SD 10), and SS: 33.5 (median value 32, SD 6). The mean LL in L1-S1 was 47.9 (median value 45, SD 12.8). Lower Lumbar Lordosis L4-S1 (LLL): 32.8 (median value 33, SD 7.6) and L5-S1 Lordosis: 19.8 (median value 18, SD 12.3).

Preoperative Clinical data

All included patients reported low back pain. Leg pain (Radicular) was recorded in 42 patients (58.3%). No motor weakness (0%) was observed while sensitive dysfunction was recorded in 12 patients (16.7%). The median preoperative ODI SCALE value was 70.2% (SD 1.6, Range 55-97), the median preoperative VAS SCALE was 7.5 (SD 1.3, Range 5-10). In Group 1, the mean preoperative ODI was 65%, median ODI was 65 (SD 15). Mean preoperative VAS scale was 8.02, median VAS 8 (SD 1.2). In Group 2, the mean preoperative

ODI was 77.8%, median ODI was 75.3 (SD 8.7). Mean preoperative VAS scale was 6.9, median VAS 7 (SD 1.2).

Intraoperative and perioperative data

Group 1:

Video assisted Miniopen anterior retroperitoneal approach in supine position was performed in all cases with a standard transverse modified Pfannenstiel incision of 5 cm [12,14]. The anterior sheath of the left rectus abdominis muscle was dissected longitudinally from the left side, about 2 mm lateral to the linea alba and the muscle retracted upward and laterally with careful blunt finger dissection. A short incision in the far lateral tract of the arcuate line allowed visualization of the retroperitoneal space. Under direct visual and endoscopic assistance (30 degrees -10 mm cold light endoscope coupled to a HDD screen) the preparation of the anterior surface of intervertebral disc was performed taking care of the inferior hypogastric plexus between the iliac vessels after coagulation of the middle sacral vein and artery. Therefore, an autostable retractor with blades was put in place. After complete resection of ALL, vertebral bodies were then mobilized with a spreader, providing posterior indirect decompression in each case **(Figure 2)**. Thirty-four (94.4%) 20° lordotic shape titanium and 2 (5.5%) 13° lordotic shape tantalum cages filled by bone graft or bone substitute (tricalcium phosphate) were implanted. **(Figure 3)**. A plate fixed with 3 screws secured each cage. Mean length of surgery was 107.4 minutes (median value 102.5, SD 29.2, Ranging from 90-120 minutes). Mean intraoperative blood loss was 188.9 ml (median value 200, SD 52.25, ranging from 150-200 ml). Intraoperative surgical complications were recorded in 2 patients (5.5%): 1 case (2.7%) of small peritoneal tear directly repaired and 1 case (2.7%) of common iliac vein bleeding treated by surgical compression and haemostatic agents. The mean hospitalization length was 6.4 days (median value 6, SD 1.1, range 6-7 days). A total of 2 blood transfusions were performed on 36 patients (5.5%). Early postoperative complications were recorded in two cases: 1 superficial haematoma conservatively treated and 1 postoperative new onset radiculopathy subsequently treated with a posterior decompression **(Table 1).**

Group 2:

Surgery was performed in all cases with a standard open posterior midline approach. Bilateral subperiosteal paraspinal muscles dissection, monolateral laminectomy and medial bilateral artrectomy were performed in all cases. Transpedicular screws positioning was performed free hands with final fluoroscopic control. Once ipsilateral neural elements have been decompressed if need, discectomy was performed and parallel "banana"-shaped titanium cages (filled of bone autograft) or tantalum cages were implanted in the most

anterior part of the interbody space to create a pivot for posterior compression in order to restore segmental lordosis. Posterior autologous bone grafting was placed in all cases. Mean length of surgery was 181,1 minutes (median value 180 SD 22, Ranging from 300-450 minutes). Mean intraoperative blood loss was 387.1 ml (median value 350 ml SD 145.5, ranging from 300-450 ml). One intraoperative surgical complication (dural tear directly repaired) was recorded (2.7%). Mean hospitalization length was 6.7 days (median value 7, SD 0.9, ranging from 6-7 days). Blood transfusions were necessary in 4 patients (11.1%). Early postoperative complication was recorded in 1 patient with residual postoperative sciatica (2,7%), conservatively managed **(Figure 1 D, E).** Intra and perioperative data are summarized in **Table 1**.

Postoperative Spino-Pelvic parameters

Group 1: mean PI 50 (median value 46.5 SD 9), PT 17.2 (median value 16.5 SD 15.7); SS 32.9 (median value 32 SD 7.7). The mean LL in L1-S1 was 46.5 (median value 45.5 SD 11), Lower Lumbar Lordosis L4-S1 (LLL): 35.2 (median value 35 SD 6) and L5-S1 Lordosis 26.3 (median value 25 SD 5.6).

Group 2: mean PI was 50.6 (median value 50 SD 7.5); PT value was 18.6 (median value 19.5 SD 6.7); SS was 31.5 (median value 33 SD 5.5). The mean LL in L1-S1 was 47.8 (median value 45.5 SD 9.8), Lower Lumbar Lordosis L4-S1 (LLL): 34 (median value 32.5 SD 17.2) and L5-S1 Lordosis 22.9 (median value 23.5 SD 5.7) **(Table 2).**

Follow-up data

In Group 1, the mean ODI value at last follow-up was 15% (median value 13, SD 7.1). The mean VAS value at last follow-up was 1.8 (median value 1 SD 1.2). The median time of returned to work was 2.4 months. Functional improvement (ODI/VAS) was recorded in 35 patients (98%) and in 1 patient remained stable. In Group 2, the mean ODI value at last follow-up was 21% (median value 20 SD 9.9). The mean VAS value at last follow-up was 2.5 (median value 3 SD 1.3). The median time of returned to work was 3.2 months. Functional improvement (ODI/VAS) was recorded in 33 patients (92%), in 3 patients (8%) remained stable **(Table 3)**. Brantigan Grade 4 or 5 was observed in all patients at the last follow-up. The presence of bone bridging into the cage or in the anterior part of the cage was observed in all patients in the two groups at final follow-up **(Figure 4)**. A delayed second surgery was necessary in 1 patient (2.7%) of Group 2 for adjacent disc disease (ADD). Preoperative sensory disturbance was persistent in 2 patients (1 in Group 1 and 1 in Group 2) at 24 months follow-up (5.5%). Preoperative radicular pain improved in 40 patients (96%) and remained

unchanged in 2 patients (4%) among the 42 patients with preoperative neurological symptoms.

Surgical considerations

A shorter surgical time was recorded in Group 1 (107.4 min) compared to Group 2 (181.1 min) with statistically significant difference ($p<0.0001$). Statistically significant ($p<0.0001$) reduced blood loss was recorded in Group 1 (188.9 *vs* 387.1 ml). No other variables between the two groups had significance (Hospitalization length: $p=0.1303$, number of postoperative blood transfusion: $P= 0.4095$, perioperative complications $P= 0.561$) **(Table 1).**

Radiological evaluation

Postoperative spinopelvic parameters were compared in the two groups. An ANOVA analysis was performed on pre and postoperative spinopelvic parameters. L5-S1 segmental increase of lordosis emerged between pre and postoperative values in Group 1 ($p <0.001$) and Group 2 ($p <0.05$) and was particularly greater in Group 1. The mean value of increase was 9 degrees (range from 4.5 to 13.75) in Group 1 and 5 degrees (from 0 to 10.5) in Group 2 **(Table 2).**

Clinical evaluation

The difference in the ODI values between pre-operative, 3 months and 12 months follow-up was significant in both groups ($p <0.001$). In Group 2 we observed a further significant improvement between 3 and 12 months ($p <0.05$) whilst in Group 1 we found an early improvement of all the scores at 3 months follow-up. No significant differences emerged between two groups at last follow-up because of persistent improving in both **(Table 3).**

Discussion

Single level L5-S1 interbody fusion is achieved through posterior or anterior techniques. The main advantages of posterior approaches are direct neural elements decompression and posterolateral grafting for fusion. The drawback may be injury of neural structures and denervation of paraspinal muscles weakening the posterior tension band [1,7-8]. The anterior approach can achieve an optimal restoration of segmental lordosis, indirect decompression with a faster recovery but with possible injuries to surrounding structures or vascular complications without significant difference in terms of fusion rate (88.6% vs. 91.9%, $P=0.23$) compared to TLIF[1-6]. We found significantly increase of segmental lordosis in ALIF vs TLIF procedures [1,10,12,13]. Over the last decade, the development of mini-open approaches has increased efficiency and safety of anterior surgery [9-14-17].

Intraoperative and perioperative data

The analysis of our data showed a significant reduction of surgical time and intraoperative blood loss in ALIF (P<.0001) when compared to TLIF. According to literature, the hospitalization length was similar in the two groups (6 days for ALIF and 7 days for TLIF)[18]. Minor intraoperative surgical complications (1 small peritoneal tears and 1 minor bleeding from common iliac vein) were recorded in 2 patients (5.5%) for Group 1 directly repaired with any consequences. One intraoperative complication (2.7%) was recorded in Group 2. Early postoperative complications were recorded in 3 patients (4.1%): 2 patients in Group 1 (5.5%) and 1 patient in Group 2 (2.7%). We observed 1 postoperative superficial haematoma (2.7%) in ALIF group that did not required revision surgery and 1 case of early sciatica for each group. Despite we did not found a significant difference between two groups, our results are comparable to findings reported in the literature (4.4% for anterior approach and 5.9% for posterior approach) [15]. In our series, 2 patients needed a second unexpected surgery: 1 patient in Group 1 for acute postoperative radiculopathy due to small disc fragment compressing nerve root, and 1 patient in Group 2 for delayed ADD at 1 y follow up. Recent studies comparing approach related complications between anterior and posterior procedures found different and conflicting results in terms of morbidity rate. Some Authors described a worst outcome in the posterior group and others concluded that anterior approaches might be associated with higher postoperative morbidity and reoperation rates than posterior ones [17-19]. Despite we found a significant increase of blood loss in the TLIF group, we did not find a significant difference in complication and reoperation rate between the two approaches (P=0.561). In our series, in order to reduce bias, we included only patients with 1 level of DDD/PDS treated by single senior surgeon, trained in anterior approaches, to limit the impact of the access related complications in both groups. All ALIF procedures were performed by video assisted mini-open exposure and that, as reported in large series, is associated with lower intra and perioperative complications [20-24] **(Table 1).**

Radiological outcomes

Significant differences regarding improvement in L5-S1 segmental lordosis (P<.0001) favoring ALIF group were observed. ALIF procedure allows powerful space distraction obtained by the ALL resection and the insertion of large and lordotic cage **(Figure 5).** We recorded a greater median value of final L5-S1 lordosis (25°) compared to real cage lordosis (13° and 20°) probably because cage acted as a pivot. In large series radiographic outcome showed a significant greater disk height (p= 0.01), segmental lordosis (p= 0.03), and an increase of whole lumbar lordosis (p= 0.03) in the ALIF group versus TLIF group [25-29]. Compared to TLIF technique, ALIF procedure is associated with a better postoperative

segmental lordosis restoration and may be a reasonable option in presence of severe DDD, when an optimal sagittal alignment should be obtained and when direct spinal canal decompression is not needed [28 30] **(Table 2).** Even if it was not the main goal of this study, at the last 2 years follow-up, we observed radiological evidence of fusion on X-Rays or CT scan (**Figures 4**) in all patients and 1 case of ADD (L4-L5) in Group 2. Complete fusion in both groups, confirmed by a senior radiologist, was somehow surprising but not unique in the literature [25-26]. A possible explanation could be that the small number of patients reduced the likelihood of observing non fused patients [12,18,21]. Furthermore, non-union could have been a possible cause of patient drop-out. These patients may have had persistent pain or other complications and thus could have referred to other centers.

Clinical outcome

The mean postoperative ODI was 25% (median value 24, SD 12) in Group 1 and 35.5% (median value 36 SD 9.3) in Group 2. ODI/VAS improvement was observed in 98% of patient in Group 1 and in 92% of Group 2 at last follow-up. Despite in TLIF group the functional improvement between 3 and 12 months was significant ($p < 0.05$), no significant differences emerged between two groups at last follow-up, as to emphasize the role of interbody fusion in the treatment of discogenic pain [1-18-20]. We found an early median time of return to work in ALIF (2.4 months vs 3.2 months) compared to TLIF. This data could be explained because of the anterior approach advantages (more anatomical) but there are not strong evidences supporting this assumption [20-22, 25] **(Table 3).**

Limits of this study

The limits are the retrospective design, the small sample size, even if homogenous. Despite we selected the pool of patients according to our standard criteria for choosing the approach, it could represent a possible selection bias that could be improved by further randomized studies. The involvement of a single Institution and, moreover, a single surgeon may be a weakness (without comparison) but also a strength (reducing technical variations or surgical bias). The rate of fusion we observed at the final follow up, confirmed by an independent senior radiologist, is anecdotal, although this was not the main goal of this study. Given the limited samples, data of fusion rate cannot be generalized.

Conclusions

Even if clinical benefit was achieved earlier in the ALIF group (faster return to work), both procedures improved functional outcomes at last follow-up without a significant difference. ALIF procedures showed significant ($P<0.0001$) lower blood loss and shorter surgical time

if compared to TLIF. ALIF allows a powerful intervertebral disc distraction with significant better segmental lordosis restoration if compared to TLIF ($P < 0.001$). Further prospective studies are necessary to evaluate in larger series complications and fusion rate, as well as possible influencing factors of ADD development between anterior and posterior approaches.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper

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FIGURES

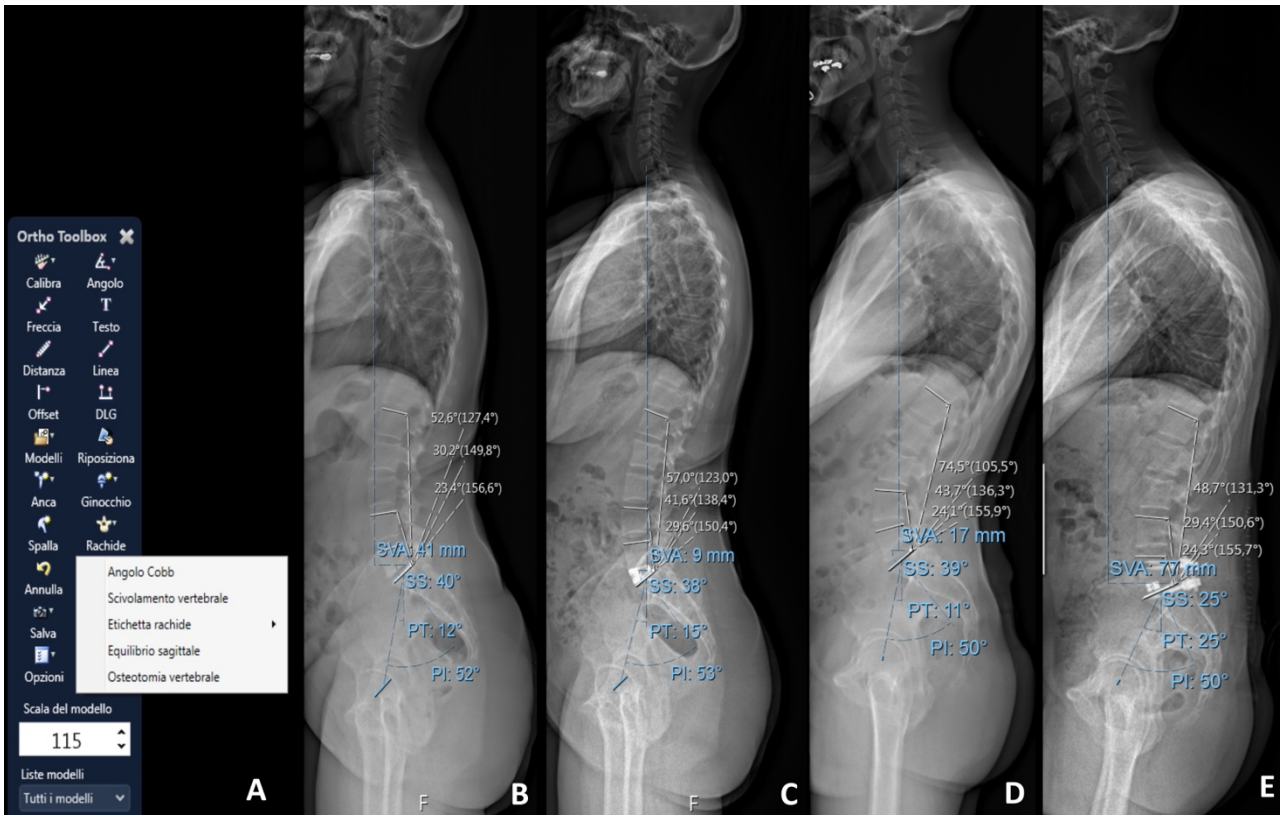

FIGURE 1: A-E: Pre and Post-operative radiological measurement of full spine-Xray in ALIF (B-C) and TLIF (D-E) groups. Pelvic incidence (PI) is measured by drawing an angle between a line perpendicular to the sacral plate at its midpoint and a line connecting the same point to the centre of the bicoxofemoral axis. Pelvic Tilt (PT) is measured by an angle between the centre of the superior S1 endplate and a vertical line. Sacral Slope (SS) is measures by an angle between the centre of the superior endplate of S1 and the horizontal plane. Lumbar lordosis are measured as the angle between upper endplate of L1 and superior endplate of the sacrum, between upper endplate of L4 and superior endplate of the sacrum and between upper endplate of L5 and superior endplate of the sacrum (L1-S1, L4-S1, L5-S1).

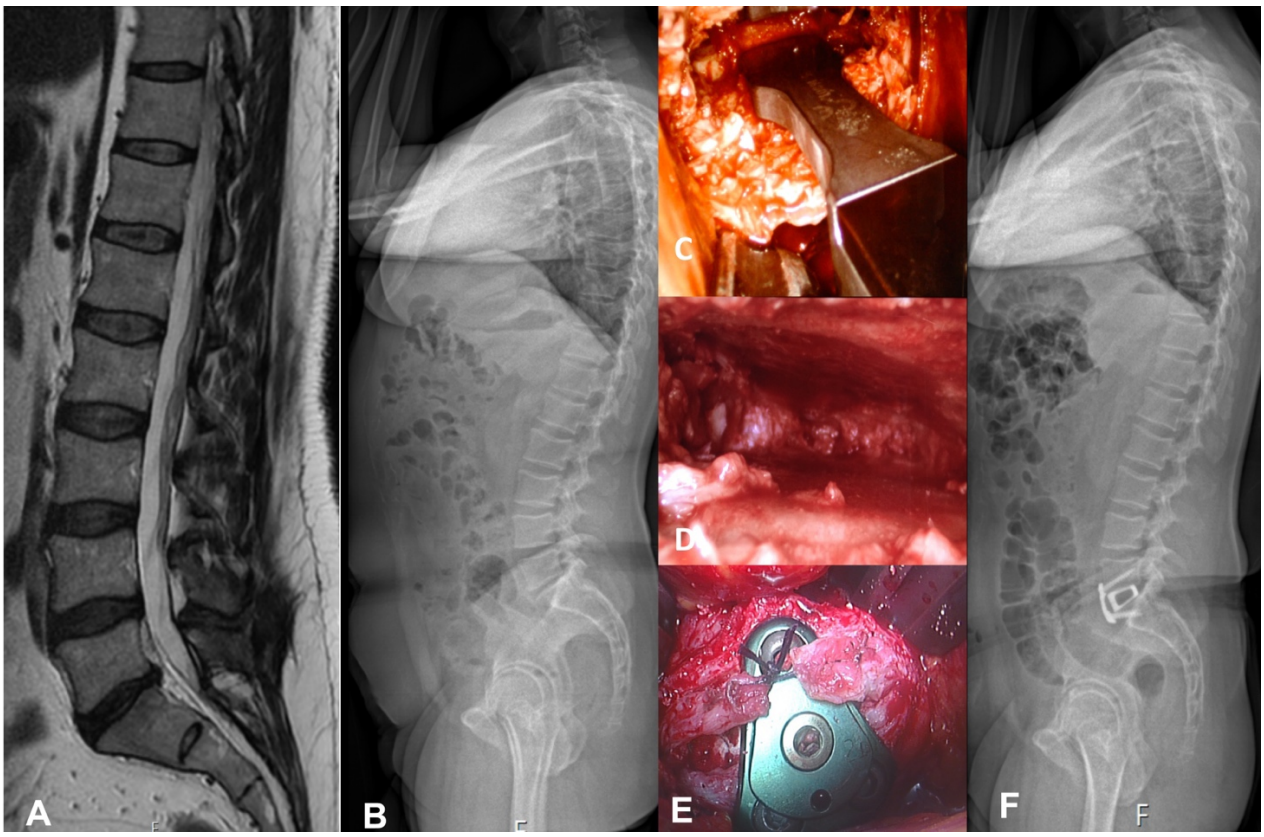

FIGURE 2: ALIF CASE EXAMPLE: **A-F:** Case example of M, 52, preoperative neurological status: low back pain and left sciatica with sensory impairment on L5 on the left, resistant to conservative treatment. **A:** T2 sagittal plane MRI showing L5-S1 Pfirrmann 4. **B:** Preoperative whole standing spine X-rays (EOS) showing normal sagittal and coronal balance. **C-D-E:** Intraoperative endoscopic view and magnification showing mobilization of the two vertebral bodies with a spreader, the posterior wall of the disc space and the two preserved anterior ligament flaps sutured together after the cage and 3 screws fixed plate implant. **F:** Postoperative whole standing spine X-rays (EOS) showing L5-S1 the correct positioning of the cage and L5-S1 lordosis.

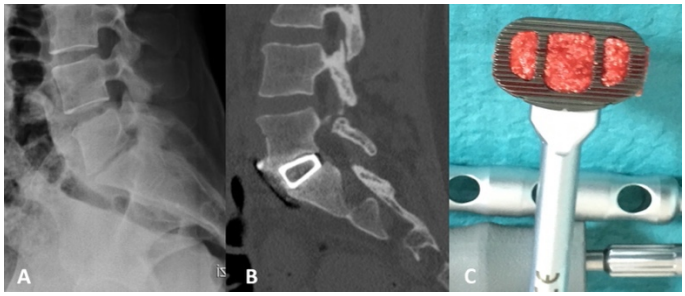

FIGURE 3: Radiological evidence of collapsed disc height and segmental lordosis restoration after anterior cage implant. A: preoperative lumbar X-Rays showing L5-S1

severe discopathy. B: postoperative sagittal CT scan showing lordotic shaped cage. C: intraoperative view of the cage filled by heterologous bone substitute.

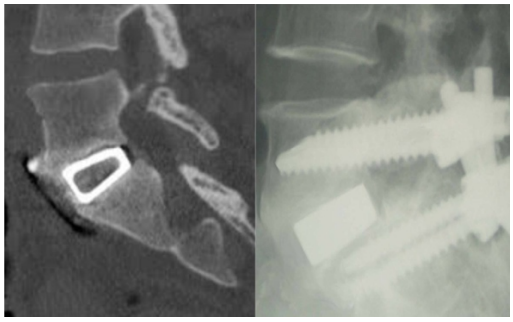

FIGURE 4: Radiological (CT scan and X-Rays) evidence of interbody fusion in ALIF (left) and TLIF **(**right**)** at the last follow-up**.** Brantigan Grade 5.

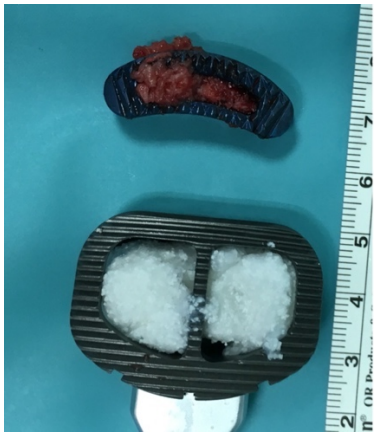

FIGURE 5: In the upper part of this figure it is shown a banana shaped titanium cage filled by autologous bone commonly used in TLIF approaches. In the lower part of the picture it is shown an ALIF lordotic shape titanium cage filled by bone substitute.

TABLE LEGEND

TABLE 1: Summary of intraoperative and perioperative data in current series

TABLE 2: Summary of radiological outcome between the two Groups.

TABLE 3: Summary of preoperative, postoperative and late Follow-up functional status according to Oswestry Disability Index (ODI) scoring systems and visual analogue scale (VAS).

TABLE 1: Intra and perioperative data

Variable	ALIF (n=36)	TLIF (n=36)	Results of statistical analysis
Sex	M:12 F:24	M:16 F:20	N/A
Age	Mean (SD): 46.09 (9,154)	Mean(SD): 50.55(13,41)	N/A
Diagnosis	DDD 31 (86%)	DDD 28 (78%)	N/A
Surgical time	PDS 5 (14%) Mean(SD): 107.4(29.2)	PDS 8 (22%) Mean(SD): 181.1(21.9)	P<0.0001
Intraoperative Blood loss	Median (IQR): 200(150-200) Mean(SD): 188.9(52,25)	Median (IQR): 350 (300-450) Mean(SD): 387.1(145.5)	P<0.0001
Intraoperative complications	5.55% (n=2)	2.7% (n=1)	P=0.561
Hospitalization length	Median (IQR): 6 (6-7) Mean (SD): 6.444(1.107)	Median (IQR): 7(6-7) Mean (SD): 6.742(0.9298)	P=0.1303
Blood transfusion	5.55% (n=2)	11.1% (n=4)	P= 0.4095
Early postoperative complications	5.55% (n=2)	2.7% (n=1)	P=0.561

N/A: not available

TABELE 2 Radiological data

Radiological outcome	Group 1 (Mean/ SD)		Group 2 (Mean/ SD)		Results of statistical analysis
	Pre-Op	Post-Op	Pre-Op	Post-Op	
PI	49.4 (11)	50 (9)	50.9 (9.7)	-50.6 87.5)	N/A
PT	16.8 (7.3)	17.2 (15.7)	17.2 (10)	18.6 (6.7)	N/A
SS	31.1 (8.3)	32.9 (7.7)	33.5 (6)	31.5 (5.5)	N/A
L1-S1 LL	-48.7 (7.3)	-46.5 (11)	-47.9 (12.8)	-47.8 (9.8)	N/A
L4-S1 LLL	-31.5 (7.5)	-35.2 (6)	-32.8 (7.6)	-34 (17.2)	N/A
L5-S1 LL	-17 (6.2)	-26.3 (5.6)	-19.8 (12.3)	-22.9 (5.7)	($p < 0.001$)

PI: pelvic incidence, PT: pelvic tilt, SS: sacral slope, LL lumbar lordosis, LLL: lower lumbar lordosis N/A: not available.

TABLE 3 Functional data

Functional outcome	Pre-Op (Mean/ SD)	Post-Op (Mean/ SD)	Last Follow-Up (Mean/ SD)	Worsened	Unchanged	Improved (%)
ODI Scale						
Group 1	65 (15)	25 (12)	15 (7.1)	N/A	1 (2%)	35 (98%)
Group 2	77.8 (8.7)	35 (9.3)	21 (9.9)	N/A	3 (8%)	33 (92%)
VAS scale						
Group 1	8.02 (1.2)	3.3 (2)	1.8 (1.2)	N/A	N/A	N/A
Group 2	6.9 (1.2)	3.4 (1.2)	2.5 (1.3)	N/A	N/A	N/A
Total	N/A	N/A	N/A	N/A	4 (5.5%)	68 (94,5) ($p < 0.001$)

ODI: Oswestry disability index, VAS: visual analogue scale. N/A: N/A: not available.

1.3 Video-assisted Anterior Retroperitoneal Approach to the Lumbar Spine. A Minimally Invasive Technique Improved by the Use of an Endoscopic Camera to Treat Lumbar Spinal Diseases. Consideration over 269 patients.

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Clinical Trial J
J Biol Regul Homeost Agents.2020 Jul-Aug;34(4 Suppl. 3):7-14.
Congress of the Italian Orthopaedic Research Society.

Abstract

We will describe the technique we personally use to perform the retroperitoneal anterior approach using a rigid endoscope (30 degrees -10 mm cold light endoscope coupled to a HDD screen) to assist mini-open retroperitoneal anterior approach. Our experience was compared to those reported in the literature for the standard mini-open retroperitoneal approach.

We retrospectively analyzed a total of 269 consecutive patients, 109 males and 160 females, underwent anterior lumbar approach in our department, using video-assisted anterior retroperitoneal approach to the lumbar spine. 202 patients had a single L5-S1 or L4-5 ALIF (75.09%), 14 patients received a double level ALIF (5.3%), while 53 patients underwent a double anterior and posterior approach (19.8%).

The average preoperative VAS and ODI scores were 9.1 ± 6.3 and 79.3 ± 11.9. At last 16 months follow-up, the average VAS and ODI values had improved to 1.6 ± 1.5 and 13.1 ± 13.2, respectively ($p < 0.05$). The mean length of stay was 4.3 ± 3.5 days. There were 6 major complications (2.2%) related to the approach: major vascular injuries (iliac vein injury) occurred in a total of 3 patients (1.1% of cases), whereas retrograde ejaculation occurred in 3 patients (2,75% of male cases in the series). No wound infections or implant

In our opinion this technique, compared with other mini-open approach, potentially reduces perioperative morbidity, length of surgery, surgical approach-related complications, and hospitalization.

Introduction

Anterior lumbar spine access is common treatment of degenerative disc disease (DDD) and chronic spinal instability as well as in failed posterior surgery [1-4]. Anterior retroperitoneal approach allows to get a direct disc space exposure to obtain a complete disc removal to perform an anterior interbody fusion (ALIF) or total disc replacement (TDR) [5]. Since the first anterior interbody placement of bone graft by Carpenter [6] the two most widely used approaches are the retroperitoneal and the transperitoneal. The retroperitoneal approach is the most commonly used as it preserves the anatomical structures of the abdomen more than the transperitoneal route [7-10]. Drawbacks of open transperitoneal or traditional retroperitoneal approaches are: size of surgical incision and possible associated tissue trauma that means more postoperative morbidity, major risk of retrograde ejaculation in male for L5-S1 dissection, hospitalization time and longer recovery period. Therefore, to decrease the risks related to the traditional approaches, several minimal invasive techniques have been developed [11-13].

In this paper we will describe the technique we personally use to perform the retroperitoneal anterior approach using a rigid endoscope (30 degrees -10 mm cold light endoscope coupled to a HDD screen) to assist mini-open retroperitoneal anterior approach. We also will compare our experience to those reported in the literature for the standard mini-open retroperitoneal approach.

Materials and methods

In this surgical technique report, we retrospectively analysed a total of 269 consecutive patients, 109 males and 160 females, underwent anterior lumbar approach in our department between January 2010 and December 2014. The mean age was 44.8 ± 10.3 years for men and 47.2 ± 10.7 years for women. The mean duration of follow-up was 16 months.

We selected patients with symptomatic DDD or symptomatic degenerative spondylolisthesis characterized by persistent or recurrent severe low back pain, with or without radiculopathy in which ALIF was performed associated or not with posterior stabilization. Patients with isthmic spondylolisthesis, or patients with an incomplete documentation or that were unable or unwilling to answer to the follow-up questionnaires were excluded.

Preoperative diagnosis, pre and post operative functional status (ODI, VAS), number of treated levels, type of surgical procedures performed, mean duration of surgery, blood loss, surgical related complications, general peri-and postoperative complications, length of stay have been collected. All patients received cycles of conservative treatment (medication, physical therapy, pain therapy) for a period of at least 6 months before surgery.

We treated 269 patients: 202 patients had a single L5-S1 or L4-5 ALIF (75.09%), 14 patients received a double level ALIF (5.3%), while 53 patients underwent a double anterior and posterior approach (19.8%).

Statistical analysis

Statistical analysis was performed in order to consider significant differences in the groups. Results were compared using the Student's T test, while analysis of variance (ANOVA) test was used to compare the results of the single groups

Surgical technique description

Each patient is positioned supine with both legs and lumbar spine in neutral position. A slight Trendelemburg position is obtained tilting the operating table, allowing the upward shift of abdominal structures. The first surgeon stands on the right side of the patient (Figure 1).

The first part of the surgery is carried out without the use of the endoscope and the main steps are no different from the standard mini-open approach. A transverse modified Pfannenstiel incision of 4 cm is made, for L5-S1 or pararectal on the left side for L4-L5. The anterior sheath of the left rectus abdominis muscle is dissected longitudinally from the left side, about 2 mm lateral to the linea alba and the left rectus muscle retracted upward and laterally with careful blunt finger dissection of the extraperitoneal space. Once the peritoneal sac has been exposed and bluntly pushed aside, a short incision in the far lateral tract of the arcuate line (Douglas Line) allows visualization of the retroperitoneal space, the psoas muscle and genitofemuralis nerve. It is mandatory to identify the ureter and the left common iliac artery and vein (Figure 2) to expose L5-S1 (medially) or L4-L5 (laterally) discs. Under direct visual and endoscopic control (30 degrees -10 mm cold light endoscope coupled to a HDD screen) the preparation of the anterior surface of intervertebral disc is performed taking care of the inferior hypogastric plexus.

L5-S1 disc is exposed between the two common iliac veins and arteries (Figure 3) after coagulation of the middle sacral vessels. In cases of L4-L5 discectomy, the left common iliac vein is retracted medially after ligation of the left ileo-lumbar vein in most of the cases. Therefore, a retractor with blades is put in place and fixed into the vertebral bone with 3 pins. The 30° endoscope allows a magnified and bright visualization of the surgical corridor, that sometimes is very deep and angled (i.e. in high sacral slope). Two flaps from the anterior ligament and anulus are prepared as lateral limit of the surgical corridor to protect

the vascular structures during discectomy and implantation. The vertebral bodies are then mobilized with a spreader, restoring the height of the intervertebral space.
At this stage, the endoscope is introduced vertically in the surgical corridor allowing direct view of the superior and inferior endplates, depending on the cranio-caudal orientation of the instrument (figure 4). A deep light source and a magnification on the screen allow the complete visualization of the procedure for all surgical team and making the endplates removal easier and more effective. In case of a posterior annular defect or extruded disc herniation, the endoscope is useful to explore the posterior edge of the disc. After completing discectomy, templates of increasing sizes are introduced to restore the optimal segmental lordosis and the definitive cage is implanted.
Anterior fusion is then performed by the implantation of a hydroxyapatite-filled porous tantalum cage secured by a plate fixed with 3 or 4 screws (Figure 5). A drain is finally inserted at the end of the procedure.

Results

All the 269 patients completed the final follow-up. All patients presented a complete data set in our database, since all the clinical data were prospectively collected. Intraoperative details as blood loss, length of surgery and hardware were obtained from clinical reports (Table 1-4).
A single L5-S1 level was treated in 186 patients (69.2%), 82 men and 104 women with mean age of 44.6 ± 9.3 years.
The mean duration of surgery was 81.9 ± 29.5 minutes and intraoperative blood loss was 91.4 ± 197.5 millilitres. The mean length of stay was 4.7 ± 2.4 days. The mean preoperative VAS and ODI values were 9.1 ± 5.9 and 78.6 ± 12.9%, respectively, whereas the final follow-up VAS and ODI values were 1.5 ± 1.5 and 12.3 ± 12.3%, respectively. There were 3 major complications related to the operation: 1 iliac vein injury, 2 retrograde ejaculations. 12 patients had postoperative anaemia.
A single L4-L5 level was treated in 16 patients (5.9%), 5 men and 11 women with a mean age of 51.9 ± 12.5 years. The mean duration of surgery was 100.5 ± 35 minutes. Intraoperative blood loss was 153.7 ± 721 millilitres. The mean length of stay was 4.5 ± 3.8 days.
The mean preoperative VAS and ODI values were 8.2 ± 1.2 and 83.6 ± 11.3%, respectively, whereas the post-operative VAS and ODI values were 1.7 ± 1.3 and 6.6 ± 8.8 %, respectively. Complications related to L4-L5 access were observed in 2 patients: 1 lesion of the left iliac vein and 1 case of retrograde ejaculation. 3 patients developed postoperative anaemia.
Two-level L3-L5, L4-S1 anterior approach was performed in 14 patients (5.2%), 1 male and 13 women with a mean age of 46.5 ± 14.7 years. 10 patients (71.4%) underwent L4-S1 anterior

interbody fusion, 2 patients (14.3%) had a L3-5 ALIF, while 2 (14.3%) had a L5-S1 ALIF plus an L4-5 TDR

The mean duration of surgery was 129.6 ± 62.4 minutes. Intraoperative blood loss was 462.1 ± 532.4 millilitres. The mean length of stay was 6.5 ± 2.4 days. The mean preoperative VAS and ODI values were 9.2 ± 0.9 and 85 ± 11.9%, respectively, whereas the post-operative VAS and ODI values were 1.4 ± 1.3 and 10.4 ± 9.1%, respectively. In this group, complications related to the approach were observed in 1 patient (7.15%) who had lesions of the left iliac vein and postoperative anaemia.

A circumferential (360°) approach was performed in a total of 53 patients (19.7%), 21 men and 32 women with a mean age of 50.2 ± 11.6 years. The mean duration of surgery (including change of position) was 232.4 ± 106.8 minutes. Intraoperative blood loss was 400 ± 263.3 millilitres. The mean length of stay was 6.6 ± 5.1 days. The mean preoperative VAS and ODI values were 8.6 ± 1.3 and 83.2 ± 8.5%, respectively, whereas the post-operative VAS and ODI values obtained were 1.6 ± 1.5 and 10.8 ± 17%, respectively. In this group, no complication related to the surgical technique was observed in any patient. 2 patients developed postoperative anaemia.

Aside from the 53 patients who had circumferential fusion, pure ALIF was performed in a total of 216 patients (80.3%). In two cases a L5-S1 ALIF was performed together with a L4-5 TDR.

The average preoperative VAS and ODI scores were 9.1 ± 6.3 and 79.3 ± 11.9, respectively. At last follow-up, the average VAS and ODI values had improved to 1.6 ± 1.5 and 13.1 ± 13.2, respectively. These differences were statistically significant ($p < 0.05$). The mean length of stay was 4.3 ± 3.5 days.

There were 6 major complications (2.2%) related to the approach: major vascular injuries (iliac vein injury) occurred in a total of 3 patients (1.1% of cases), whereas retrograde ejaculation occurred in 3 patients (2,75% of male cases in the series). No infections of the surgical wound or of the implant were observed during the follow-up.

Comparing these groups with ANOVA test, we noticed a statistically significant difference ($p<0.001$) in surgical time, intraoperative blood loss, postoperative blood transfusions, and length of hospitalization.

Discussion

The value of mini-open techniques compared to traditional approaches in terms of reduction of perioperative complications and reduction of operative time has been widely

reported in the literature [12-14]. The differences between standard mini open ALIF and video assisted technique mainly consists in the use of a 30° endoscope during the dissection, discectomy and implantation phases.

Compared with other mini-open techniques the video assistance allows a greater magnification and brightness of the surgical field. The 30° angulated camera allows a better view during dissection in multilevel approach and in the discectomy phase in a single level approach, with a complete visualization of endplates, annulus and posterior edge, in order to obtain accurate preparation of the disc space. In our practice endplates preparation under direct visual control, is one of the most important step of this approach, in order to improve fusion rate, find the best cage fit, restore the ideal lumbar lordosis giving an adequate anterior support. Disc decompression is performed under continuous visualization reducing surgical time and risk of complications especially in multilevel operations. Moreover each operator (assistants, scrub nurses) can see the screen following every single step of the procedure that means better coordination and collaboration among surgeons and medical staff.

With this video assisted technique access-related complications rate is not significantly different to those reported in the literature. We had 1.1% of vascular complication such as iliac vein laceration and 2.75% of retrograde ejaculation, whereas in the literature vascular complication rate ranges from 1.9% to 18%, retrograde ejaculation from 0.44 to 25% in standard mini-open approaches [15-19]. None of our mini-open surgeries have been commutated to an open procedure.

According to Kaiser et all an L5-S1 ALIF is associated with the shorter procedures time when using the mini-open approach (171.9 versus 185.0 minutes of the traditional approach) [13]. Our mean time for L5-S1 surgery is slightly inferior (81.9 ± 29.5 minutes), showing how the use of the endoscope doesn't increase operative time. Escobar et al. reported that the duration of surgery for a single-level fusion was 170 minutes in patient operated with a retroperitoneal endoscopic technique for a single level fusion. In case of two or more levels of fusion the operative time was 272 minutes [20]. Our mean time for two levels approach is slightly inferior (129.6 ± 62.4 minutes). Moreover, our L5-S1 ALIF group showed further less intraoperative blood loss than the other groups (91.4 ± 197.5, $p<0.001$) and this data are similar to other mini-open approach and are better than the traditional approach (range from 55 to 153 mL) [14]. In our series the average hospital stay for single level surgery was 5 days (range from 4.7 to 5.5) whereas in other series is 7.5 days for the same surgery (range, 6-10 days) [15-21].

Considering the surgical-related complications, the results observed in our population show a low overall ratio (1.1% of major bleeding and 2,75% of retrograde ejaculation).

To avoid or reduce significantly retrograde ejaculation, we perform the hypogastric plexus dissection using small cotton pads when necessary displacing laterally the plexus. [11-13]. We use bipolar forceps (never monopolar) for coagulation of the small vessels.
Our study, even if it encloses a huge number of patients and is just a surgical technique report, shows some limits: the retrospective analysis decreases the power of the study, and the length of follow-up is too short to evaluate fusion rates.

Conclusions

The mini-open video assisted approach is useful during dissection of retroperitoneal space, discectomy and implantation of the cages, allowing a magnified and bright visualization of the deep structures. In our experience this technique potentially reduces perioperative morbidity, length of surgery and hospitalization as well as surgical approach-related complications.

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TABLES:

Patients	186 M = 82 F = 104

	Age (avg. In years) 44.6 ± 9.3
Duration of surgery (min)	81.9 ± 29.5
Blood loss (ml)	91.4 ± 197.5
Lenght of stay (days)	4.7 ± 2.4
VAS (preop and postop value)	9.1 ± 5.9, 1.5 ± 1.5
ODI (preop and postop value)	78.6 ± 12.9%, 12.3 ± 12.3%
Complications, technique related Left iliac vein lesion	1
Retrograde ejaculation	2
Complications, postop Postoperative anemia	12

Table I: Group 1 description, L5-S1 anterior approach

Patients	16 M = 5 F = 11 Age (avg. In years) 51.9 ± 12.5
Duration of surgery (min)	100.5 ± 35
Blood loss (ml)	153.7 ± 721
Lenght of stay (days)	4.5 ± 3.8
VAS (preop and postop value)	8.2 ± 1.2, 1.7 ± 1.3
ODI (preop and postop value)	83.6 ± 11.3%, 6.6 ± 8.8 %
Complications, technique related Left iliac vein lesion	1
Retrograde ejaculation	1

Complications, postop Postoperative anemia	3

Table II: Group 2 description, L4-5 anterior approach

Patients	14 M = 1 F = 13 Age (avg. In years) 46.5 ± 14.7
Duration of surgery (min)	129.6 ± 62.4
Blood loss (ml)	462.1 ± 532.4
Lenght of stay (days)	6.5 ± 2.4
VAS (preop and postop value)	9.2 ± 0.9, 1.4 ± 1.3
ODI (preop and postop value)	85 ± 11.9 %, 10.4 ± 9.1%
Complications, technique related Left iliac vein lesion	1
Retrograde ejaculation	0
Complications, postop Postoperative anemia	1

Table III: Group 3 description, two levels anterior approach

Patients	53 M = 21 F = 32 Age (avg. In years) 50.2 ± 11.6
Duration of surgery (min)	232.4 ± 106.8
Blood loss (ml)	400 ± 263.3
Lenght of stay (days)	6.6 ± 5.1

VAS (preop and postop value)	8.6 ± 1.3, 1.6 ± 1.5
ODI (preop and postop value)	83.2 ± 8.5 %, 10.8 ± 17%
Complications, technique related Left iliac vein lesion	0
Retrograde ejaculation	0
Complications, postop Postoperative anemia	2

Table IV: Group 4 description, combined anterior-posterior approach

FIGURES:

Figure 1

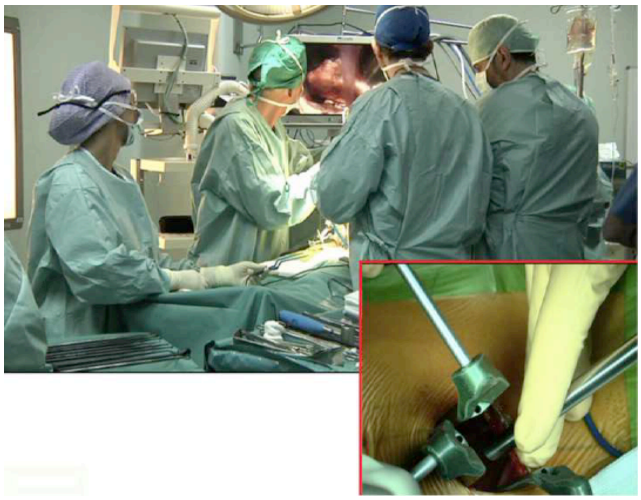

Figure 1: Intraoperative disposition of the surgeon and his assistants. Notice how the monitor
shows the deep structures (in this case the intervertebral space) that are recorded by the endoscopic camera, shown in the box on the right

Figure 2

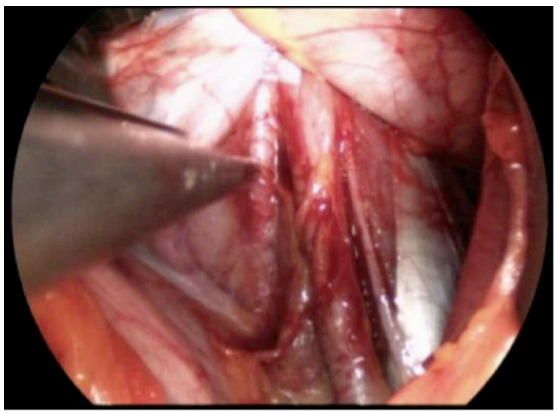

Figure 2: Intraoperative endoscopic view of ureter (indicated with an anatomic claw) and common iliac artery (on the right)

Figure 3

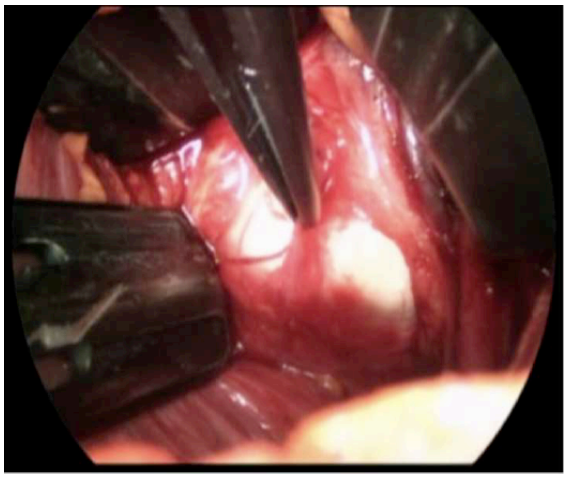

Figure 3: Intraoperative endoscopic view of the disc exposition and of the middle sacral vessels (pinched with an anatomic claw)

Figure 4

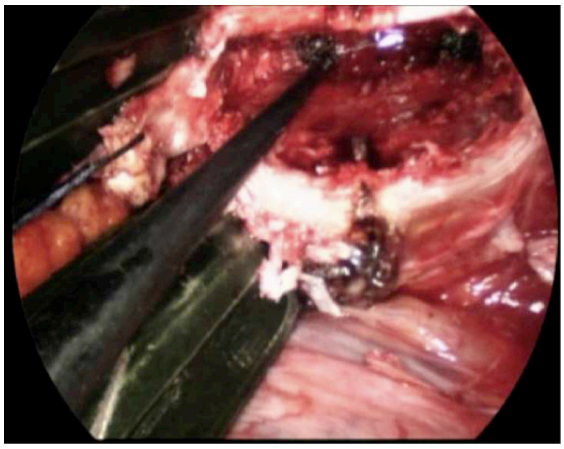

Figure 4: Intraoperative endoscopic view of the intervertebral space preparation. A sharp

instrument is used to remove the cartilagineous layer of the endplate.

Figure 5

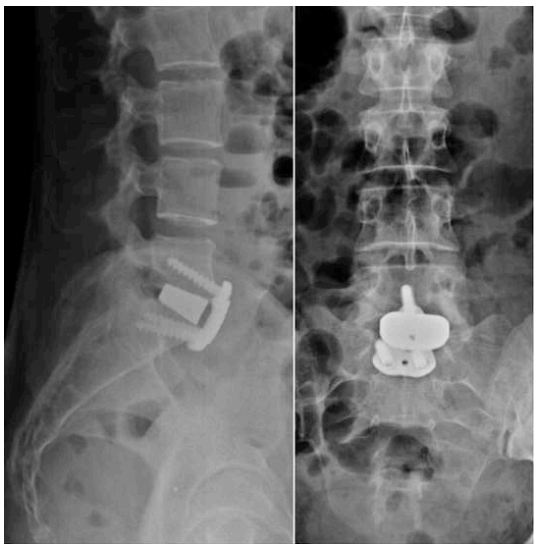

Figure 5: Postoperative x-ray (lateral and AP views) of an L5-S1 ALIF. The patient has been treated with a tantallum cage and a three-screw anterior plate. This construct has the same stability than an anterior cage with four pedicle screws.

Fig 6

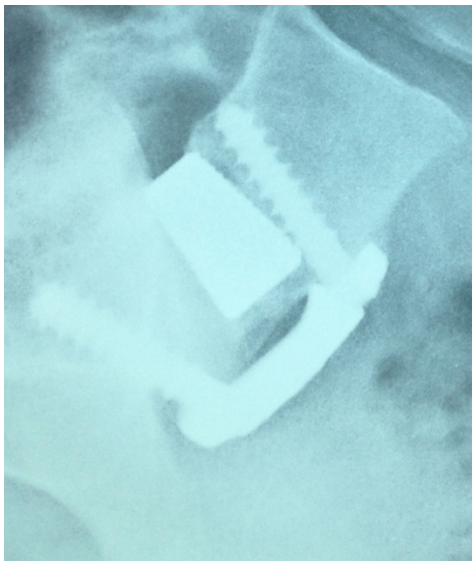

Figure 6: 1 years-follow-up lateral X-Ray of an L5-S1 ALIF showing the occurred fusion of the construct

1.4 Use of lordotic cages in L5-S1 Anterior Lumbar Interbody Fusion (ALIF) procedures

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Clinical Trial J
Biol Regul Homeost Agents
Jul-Aug 2020;34(4 Suppl. 3):23-28. Congress of the Italian Orthopaedic Research Society.

Abstract

Anterior Lumbar Interbody Fusion (ALIF) has gained popularity in the last years, thanks to its numerous advantages. Recently the use of hyperlordotic cages has been described, allowing theoretically a better lordosis restoration of the lumbar disc space. We described the results obtained with the use of hyperlordotic cages in 27 patients who underwent ALIF procedure for L5-S1 disc degenerative disease, in terms of segmental lordosis and global lumbar lordosis changes.

Introduction

Anterior Lumbar Interbody Fusion (ALIF) is a surgical technique for spinal fusion that encountered an increasing interest by spinal surgeons (13).
The evolution of this surgical technique, from the first description to the minimally invasive "perinavel" approach (4) has recently been published (3). The use of the anterior access allows the surgeon to have access to the disc space, avoiding traumas to paraspinal muscles and the formation of epidural scarring and fibrosis (17,18,25).
Many studies have demonstrated the superiority of ALIF if compared to Transforaminal Lumbar Interbody Fusion (TLIF) in terms of disc height, segmental lordosis (SL) and lumbar lordosis (LL) restoration (1,12,14,19).
The cages used in ALIF approach have traditionally a certain degree of lordosis, between 8 and 12 degrees (22). In the last years the use of hyperlordotic cages has been described, ranging up to 30 degrees of lordosis (7,11,23,24).

Aim of this study is to determine the increase in segmental lordosis at the L5-S1 segment with the use of hyperlordotic cages in patients with L5-S1 degenerative disc disease.

Materials and methods

We have analyzed 27 cases of patients who underwent ALIF for degenerative disc disease at the L5-S1 level between January and December 2018. The study was centered on the evaluation of SL and LL before and after the ALIF procedure, performed with the use of hyperlordotic interbody cages.

Inclusion criteria were: L5-S1 degenerative disc disease as the cause of low back pain (with or without radicular pain), once all other possible causes were excluded; failure of conservative treatment over a period of at least 6 months. Exclusion criteria were: presence of lumbar scoliosis (Cobb > 20°), presence of infectious or tumor disease, previous fusion at the same or other lumbar levels, presence of spondylolisthesis or isthmic lysis.

All patients have been investigated with a lumbosacral Magnetic Resonance Imaging (MRI) and a lumbosacral radiograph in the preoperative, immediate postoperative and during follow-up at 6 months (when possible the patients were investigated with a full-spine standing radiograph with EOS imaging ®).

All patients underwent surgery with a video-assisted surgical technique, as previously described by the senior author (2), and the mini-ALIF procedure was performed in all patients at the L5-S1 level with an hyperlordotic interbody implant and plating through a retroperitoneal surgical route.

Segmental lordosis in L5-S1 has been analyzed preoperatively, in the immediate post-operative and during follow-up at 6 months to evaluate eventual subsidence.

Intraoperative and postoperative complications have been recorded.

Results

The study included 27 patients, 9 males (33.3%) and 18 females (66.7%). The mean age was 46.9 ± 10.5 years, range 29-72. The mean length of the hospital stay was 4.8 ± 1.2 days.

No infections were registered. In 2 cases during the approach was observed a peritoneal lesion, repaired with a suture and without further complications in the postoperative period. No vascular injuries were registered. In male patients no cases of retrograde ejaculation have been encountered. There were no cases of thrombophlebitis during follow-up. The mean L5-S1 SL was 8.5 ± 3.8 degrees (range 2.4-15.1) in the preoperative period. After the ALIF procedure the mean L5-S1 SL was 21.5 ± 3.8 (range 13.5-30.0) in the immediate post-operative period and 21.4 ± 3.8 (range 13.3.30.0) at the 6 months follow-up.

The difference between the preoperative SL and the immediate postoperative SL was statistically significant ($p < 0.001$). The mean increase in SL was 12.9 degrees (range 4.0 – 23.9). The difference between the preoperative value and the follow-up value was also statistically significant ($p<0.001$). The difference between immediate postoperative and follow-up values was not statistically significant ($p=0.58$).

A linear regression test showed a negative relationship both between preoperative SL and the absolute variation in L5-S1 SL ($r2=0.484$) and between the preoperative SL and the percentage variation in SL if compared to the preoperative SL ($r2=0.804$).

The mean preoperative LL was 54.1 ± 9.0 degrees (range 36.9 – 67.9). In the immediate postoperative the mean LL was 53.0 ± 8.8 degrees (range 32.6 – 70.4) and during follow-up the mean LL was 60.0 ± 9.3 degrees (range 39.6 – 79.6) (see Table 1). There difference between LL in preoperative and immediate postoperative was not statistically significant ($p=0.45$). A statistically significant difference is noticed between preoperative and follow-up LL and immediate postoperative and follow-up LL ($p<0.001$).

Discussion

In our study we focused on the segmental change in lordosis in L5-S1 disc in patients with degenerative disc disease and low back pain who underwent fusion with hyperlordotic anterior cages. ALIF seems a viable option to restore segmental lordosis at L5-S1 disc space, with optimal results.

The capability of ALIF to restore segmental lordosis has been widely described in literature during the years. Lateral Lumbar Interbody Fusion (LLIF) is usually not able to reach the L5-S1 disc space, therefore it would not be considered in the discussion.

Before the introduction of hyperlordotic cages, ALIF was considered superior to TLIF in both disc height and segmental lordosis restoration. Previous studies reported a mean variation in SL of 8.3°(12) and 8.6°(16). In our study the mean variation in SL was 12.9°. This demonstrates a higher power of SL restoration if compared to the older Interbody implants.

The few studies published involving the use of hyperlordotic ALIF cages are focused on the correction of sagittal imbalance with multilevel cages, and anterior cages are supplemented with posterior instrumentation (7,11,24). Therefore, they do not analyze the difference in SL variation related to the use of hyperlordotic cages. A higher increase in L5-S1 SL might help to better manage the lack of lordosis.

Previous studies (12) reported an increase in LL of 6.2° after ALIF fusion. The results of our study showed an increase of LL between preoperative values and 6 months follow-up of 5.9°. Surprisingly the mean LL in the immediate postoperative period was 1° inferior to the

preoperative values. This might be interpreted as a remodeling of LL during follow-up related to the loss of postoperative muscular contraction. A non statistically significant difference between L5-S1 LL between immediate postoperative and follow-up demonstrates a scarce tendence towards cage subsidence, at least in a 6-months follow-up period.

Theoretical advantages of the anterior approach over the posterior one has been advocated. It is a muscle sparing technique, avoiding posterior muscle detachment and denervation. The direct approach to the disc space (as in the anterior approach to the cervical spine) allows to perform a complete and accurate discectomy; the resection of the anterior longitudinal ligament permits a wider distraction with better disc height restoration and foraminal height increase. Finally, the implant of hyperlordotic implants might help in better managing sagittal profile restoration (5,9–11,15,17,18,21).

On the other side, the most frequently described complications include vascular, bowel and ureter injuries, retrograde ejaculation, peritoneal lacerations, ileus, retroperitoneal hematoma, herniation through the abdominal wall, arterial and venous thrombosis (6,8,17,20).

ALIF has become increasingly popular thanks to its numerous advantages over the posterior approach. It allows to reach better results in terms of SL if compared to TLIF technique. The higher power of SL restoration might be helpful in both short segment fixation and sagittal balance restoration in those cases of major sagittal deformity.

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	Preoperative	Immediate PO	Follow-up
Mean SL	8.5 ± 3.8	21.5 ± 3.8	21.4 ± 3.8
Mean LL	54.1 ± 9.0	53.0 ± 8.8	60.0 ± 9.3

Table 1: mean values of Segmental Lordosis (SL) and Lumbar Lordosis (LL) in preoperative, immediate postoperative (PO) and follow-up.

1.5 New trends in spinal surgery: less invasive anatomical approach to the spine. The advantages of the anterior approach in lumbar spinal fusion.

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Rewiew article
Turk Neurosurg. 2021;31(4):484-492.

Abstract

Aim: The purpose of this review is to describe the history of the anterior approach to the lumbar spine from the beginning to the minimal invasive techniques we have developed discussing its advantages and drawbacks.

Material and methods: The Authors collected published data on the evolution of the anterior approach in the lumbar spine, and described its potential in different pathologies focusing on minimally invasive techniques.

Results: Several successful techniques of anterior lumbar approach have been developed over the years, leading to a progressive less invasive anatomical exposure of the spine. Anterior approaches of the lumbar spine gained popularity as an alternative to posterior routes in the management of tumors, infections, traumas, degenerative or deformity diseases and as a salvage procedure after posterior surgery.

Conclusion: Advantages of the retroperitoneal anterior approach of the lumbar spine are well accepted: it preserves the anatomical structures of the abdomen and posterior tension band, avoiding muscle dissection. The implantation of lordotic cages with larger footprint improves local lordosis and fusion rate even in revision surgery. Drawbacks of traditional retroperitoneal approaches may be: vascular injury, deep venous thrombosis, risk of retrograde ejaculation in male in case of L5-S1 dissection. Therefore, , several minimal invasive techniques have been developed to decrease the risks related to the traditional approaches. However, a long learning curve is required to achieve good skills and to manage possible technical concerns and complications.

Introduction

Anterior lumbar interbody fusion (ALIF) is currently one of the most important approach to achieve interbody fusion for lumbar spinal disease among the available techniques (3,5). Degenerative conditions of the spine, severe flat-back (iatrogenic or degenerative), surgical revisions, and infections are the main indications of anterior lumbar surgery (5). The purpose of this review is to describe our experience in minimally invasive techniques, starting from the history of the anterior approach of the lumbar spine to the minimal invasive techniques we have developed.

Evolution of the anterior approach

In the early 19th century pioneer surgeons, driven by a desire to find surgical solutions to treat Pott's disease, laid the foundations of anterior lumbar fusion surgery (17,18,23).

In the 1932 Capener et al. (10) described for the first time a theoretical access to the anterior lumbar spine in a case of spondylolisthesis. Consequently, successful practical evolution of this approach was derived. The boost to develop anterior routes started as an alternative to posterior approaches in the management of tumors, infections, traumas, degenerative diseases, and as a salvage procedure when posterior grafting was inadvisable (9,21,28). Burns et al. described a tibial autologous bone graft inserted using a transperitoneal approach through L5 wedge for the first time in 1933 (9). Mercer et al. performed the first interbody L5-S1 fusion with the same approach (21). Due to drawbacks and high surgical morbidity of open transperitoneal approaches (large skin incision, abdominal muscle trauma and major risk of retrograde ejaculation in male affected by L5-S1 dissection), less invasive routes have been explored and anterior interbody fusion (ALIF) technique gained new popularity in the 1980s (11).

Laparoscopic transperitoneal and mini-open retroperitoneal approaches have been then proposed to preserve the muscular integrity and function of the abdominal wall (12,19,20,24). However, laparoscopic techniques presented several drawbacks related to loss of depth perception, the use of CO2 insufflation with several complications, and a long learning curve. Thus, this approach was soon abandoned (12,19, 24).

The anterior mini-open retroperitoneal exposure has acquired consensus as it causes less complications with better results. A muscle-sparing technique was optimized to reduce postoperative surgical morbidity, hospitalization, and rehabilitation time (3, 20).

Along with the development of less invasive anterior lumbar exposures, less invasive skin incisions have been described for single or multilevel procedures (3).

The classical median, paramedian or S-shaped skin incisions from the symphysis to the umbilicus have been progressively replaced by single transverse or pararectal shorter skin incisions in the lower third and the middle lower abdominal quadrant to expose retroperitoneal space (3) (FIGURE 1).

The anterior mini-open retroperitoneal approach requires a Pfannestiel skin incision less than 5 cm to expose the L5-S1 space (FIGURE 1 A). Alternatively, a pararectal skin incision on the left side is generally performed to expose the L4-L5 space. Left side is usually preferred due to easier mobilization of the left iliac vein and artery during dissection (from the right side common iliac vein or vena cava should be first mobilized especially for L4-L5 or higher spaces) (6). Multilevel ALIF exposures were traditionally performed using huge or multiple muscular and fascial incisions, with possible drawbacks, thus the need of suitable surgical incision has become crucial (3).

To reduce the invasiveness on muscular and fascial tissues, we recently proposed the original "keyhole" perinavel skin incision for a minimally invasive exposure of both single (i.e. L5-S1 or L4-L5 or L3-L4) and multiple levels (from L2-L3 to L5- S1), all in the retroperitoneal space (14) (FIGURE 1 B-C).

We performed a 270° perinavel incision using Colorado ® microdissection needle (FIGURE 1-B). The subcutaneous fatty tissue is then exposes with a semicircular dissection to produce a large fatty pad layer below the umbilicus, thus preserving superficial and deep vascular supply. The subdermal plexus (superficial blood supply) originates from the superficial superior and inferior epigastric arteries. The deeper vascular sources originate from the right and left deep superior and inferior epigastric vessels, the ligamentum teres hepaticum and the median umbilical ligament. Some perforating branches connect superficial and deep system, supplying the ventromedial skin of the lower area of the chest wall and the superior and periumbilical abdominal wall. Given this topographic vascular distribution, a 270° skin incision (inverse horseshoe shaped skin incision) preserves vascular anastomosis saving for 90° the superior part of the umbilicus; thus, it avoids umbilical necrosis (FIGURE 1).

To spare abdominal wall muscles, the anterior sheath of the left rectus abdominis muscle is longitudinally sectioned from the left side, about 2 mm lateral to the linea alba, and the left rectus muscle is retracted upward and laterally with careful blunt finger dissection of the extraperitoneal space. Once the rectus muscle is retracted, it is important to avoid tractions or lesions of the inferior epigastric vessels, which are located on the posterior side of the muscle. The peritoneal sac is then exposed and bluntly mobilized. The most lateral tract of the arcuate line (Douglas Line) is sectioned or bluntly dissected to expose the retroperitoneal space. The psoas muscle and genitofemuralis nerve are then visualized. During this step, the identification of the ureter, the left common iliac artery and vein is essential to localize

and expose the L5-S1 disc (generally between iliac bifurcation), or the L4-L5 disc (laterally to the left common iliac vessels) (3). In multilevel ALIF procedures using the "keyhole" perinavel skin incision, we usually first approach the most inferior disc space and then we proceed cranially up to L2, if needed (FIGURE 1 C).

In patients with high sacral slope (i.e high grade dysplastic spondylolisthesis), a less favorable inclination of the surgical field can cause an excessive traction of the cutaneous tissues; thus, careful dissection of each layer is mandatory to reduce tension.

Once the L5-S1 disc is exposed, the common iliac vessels are retracted and protected; finally the middle sacral vessels are ligated to avoid injury to the inferior hypogastric plexus (IHP). Coagulation with bipolar forceps could produce thermal or electrical injury to IHP. The utilization of the monopolar knife must be avoided.

Once vessels are mobilized and complete exposure of the disc is performed, hemostatic agents with oxidized cellulose (Surgicel®) are placed behind each retractor blade to protect the veins. The retracting blades are generally fixed to the vertebral body with dedicated pins. This very stable configuration avoids the risk of soft tissue or vascular injury due to retractor's accidental movements during discectomy or cage implant. An autostable ring is then placed to connect the handles of the retracting blades to obtain a 360 degree stability and a complete view of the surgical field.

More vertical and favorable surgical corridor is encountered above L5. Aorta, cava and common iliac veins and arteries are retracted from the left to the right side towards the midline. To avoid traction or tears, ligature of the ileolumbar vein is often necessary.

Subsequently, aorta is medially displaced to expose the lateral aspect of the L3-L4 space. Segmental vessels from the aorta and vena cava on the anterolateral aspect of the vertebral body should be carefully identified and ligated.

In our series, using perinavel approach, postoperative complications' rate related to skin incision was 4,12% (3) and all the complications were conservatively managed. The rate of venous injury with the single "keyhole" perinavel incision was similar to the current literature (3.09% vs. 3.07%), demonstrating its safety compared to traditional approaches (6). A single perinavel incision, acting as a "sliding door" to the retroperitoneal space, allows for a better exposure of the anterior midline of the lumbar spine. Moreover, this technique reduces postoperative abdominal pain, abdominal morbidity, and blood loss allowing for a shorter postoperative recovery, bed rest and length of hospitalization if compared to other incisions.

Further innovative techniques

In the last decades autologous bone grafts used as "spacer" and fusion devices have been replaced by other special devices with different footprints, size and lordotic shapes (titanium, peek, tantalum, and other allograft cages). Dedicated deeper autostable retractors with special blades have been designed to obtain optimal visualization of the surgical field. To reduce operative time and complications, we usually recommend the use of video assistance to perform better disc preparation and cage implantation (4) (FIGURE 2).

Once anterior interbody surface has been prepared and the autostable retractor fixed, a rigid endoscope (30° -10 mm cold light endoscope coupled to a High Definition -HD screen) allows for a better view of all phases of disc preparation both in single and multilevel approaches. The anterior longitudinal ligament (ALL) is then sectioned to create two lateral flaps protecting the surgical corridor. After a complete discectomy, the deep light source allows for a complete endplates visualization, until the posterior annulus. A complete and accurate discectomy is one of the most important step to obtain the fusion (FIGURE 3A-F). Furthermore, the HD screen visualization permits a better coordination and quicker collaboration among staff components (assistants, scrub nurses), reducing operation time (4).

In our experience, the video assisted mini-open retroperitoneal anterior approach does not significantly increase the access-related complications' rate compared to the current literature (4). On 269 patients, we registered 1.1% of vascular complication (venous) and 2.75% of retrograde ejaculation in males; whereas in the literature vascular complication rate ranges from 1.9% to 18%, retrograde ejaculation from 0.44 to 5% in standard mini-open approaches (7,15,16, 26, 27).

ALIF in degenerative Lumbar Spinal disease

Despite the initial higher drawbacks of the anterior approach compared to potential benefits, the subsequent progressions to safer and advanced techniques have increased ALIF usefulness as an alternative procedure to standard posterior approaches, especially in case of degenerative diseases (1, 3, 11). Mechanical low back pain can origin from disc degeneration or facet joints' arthritis. Disc degeneration due to nucleus progressive dehydration and recurring annulus injuries can lead to a symptomatic progressive disc height reduction, and ultimately to complete collapse of the disc. Facet joint arthritis, legamentum flavum hypertrophy, and the concomitant osteophytes in presence of posterior tension bend weakness can cause degenerative instability with secondary canal stenosis.

Spinal interbody fusion (IF) has been widely recognized to improve clinical outcome in surgical treatment of degenerative pathology of the lumbar spine (5).

ALIF is actually employed in the surgical treatment of degenerative disc disease (DDD), in spondylolisthesis (both degenerative and isthmic), or to achieve fusion in recurrent lumbar disc herniation and post-discectomy kyphosis with good results even in terms of proper lumbar lordosis restoration (FIGURE 4-6) (3, 5).

According to our experience in the management of a single level L5-S1 DDD, ALIF showed better results compared to trans foraminal interbody fusion (TLIF) in terms of surgical (lower blood loss and shorter surgical time), radiological (SL improving) and clinical (early postoperative pain reduction) outcomes (5).

In the treatment of DDD as well as in recurrent lumbar disc herniation and post-discectomy kyphosis ALIF approach avoids muscle denervation and fat degeneration (5). Furthermore, the fusion rate can be increased by placing the cage anteriorly, in the bony surface area that supports about the 80% of axial load in the upright standing position. In the management of degenerative spondylolisthesis, ALIF corrects disc height and it stabilizes the anterior column. Compared to posterior IF, a direct anterior approach to the disc allows for restoring an optimal segmental lordosis (SL) as well as an open foraminal spaces, leading to an indirect decompression of the nerve roots (5).

ALIF in the correction of sagittal alignment and revision surgery

Anterior approach gained further popularity among spine surgeons in the treatment of complex spinal disease like adult spine deformity (ASD) and revision surgery (FIGURE 7-8) (1, 5), due to the development of lordotic and hyperlordotic shaped cages. The goal of a complex correction of a spinal deformity in adulthood and of a revision surgery is to improve the quality of life (QoL), achieving sagittal and coronal imbalance correction to get a stable spinal fusion and pain relief. Several studies demonstrated that the loss of lumbar lordosis (LL) can lead to sagittal malalignment with QoL impairment (1). Therefore, ideal lumbar lordosis restoration and the bony fusion represent the most important aims of the corrective surgery.

Traditionally, cages used in anterior approach have between 8 and 12 degrees of lordosis (2). Recently, multilevel cages (with lordosis from 15° to 30°) have been adopted to correct sagittal malalignment with significant improvement of SL instead of huge posterior pedicle subtraction osteotomies (2).

ALIF safety and efficacy in ASD surgery have been well documented (1, 5) in the treatment of pain due to sagittal imbalance and in residual hypolordosis after failed posterior fusion (13, 22).

The ALL resection with an anterior surgical approach allows for a direct vision to the disc. After a complete discectomy and posterior annulus release, a powerful interbody

distraction permits an optimal disc height restoration and foraminal decompression. The implantation of a large and lordotic cage provides great primary stability, increasing potential fusion rate and restoring SL (FIGURE 4) (2, 5). In presence of posterior hardware, a strong anterior support permits to overpower posterior instrumentation avoiding osteotomies and reducing surgical time and perioperative blood loss (FIGURE 9)(13).

The capability of ALIF to restore SL and to correct sagittal imbalance has been widely described in the literature during the years (5). Many studies have demonstrated the superiority of ALIF compared to TLIF in terms of disc height and LL restoration (5).

ALIF procedure in ASD surgery is particularly indicated in presence of loss of LL between L4–S1 (21). The ideal proportion of LL increased gradually, from 4% for L1-L2 to 35% for L5-S1 (2). Double or multilevel ALIF offers an harmonic and graduated correction of the LL avoiding injury of the posterior muscle tension band (1). Thus, the perinavel approach, working as a "sliding door", allow for performing single stage multilevel ALIF from L2 to S1 with a lower rate of complications (6).

ALIF procedure achieves SL restoration with lower complications and higher fusion rates compared to posterior osteotomies (13). These advantages should be carefully considered in the planning of ASD or revision surgery.

The anterior exposure of lumbar discs can also be useful in the revision surgery of unsuccessful posterior interbody fusion due to loss of SL, cage nonunions, mobilization or infection. Posterior approach can cause perineural scarring tissues, thus it may increase the risk of dural tear, nerve root injury or infections. Anterior naive approach to the disc can limit these complications with a powerful correction of local kyphosis (3, 22).

ALIF complications and their management

Despite the recent ALIF popularity among spinal surgeons, the potential risk to injure retroperitoneal or intra-peritoneal structures remains consistent; therefore, its application requires a long learning curve (26).

Complication rate of ALIF procedure has been highly variable, accounting between 8.4 to 31.1% in the large series depending on differences in complication endpoints reported in the studies and on heterogeneity of surgeries (i.e., single-level or multilevel ALIF) (14, 25).

The main concerns of this approach are vascular injuries and retrograde ejaculation (RE) (7, 8, 15, 25, 29).

Intraoperative venous injuries (usually left iliac vein), occurs between 1.9 to 18% in large series, and mostly occurs during L4-L5 exposure (iliolumbar vein tear) (7).

To avoid injuries during disc exposure, we recommend a careful mobilization of the artery and vein starting as distally as possible without mechanical stresses. In case of

spondylolisthesis or anterior revision surgery, careful removal of all fibrous tissue between the anterior spinal surface and veins is crucial. The iliolumbar vein or L4 segmental vessels should be always identified, mobilized and often ligated to avoid tears at the junction to the iliac vein, thus facilitating anterior exposure of L4-L5 disc space.

If vein injury occurs during exposure, early identification and bleeding control should be promptly performed with vein compression or suture repair. In cases of small tears (< 3 mm), compression and hemostatic agents generally can control more than 90% of the bleeding and suturing may not be required. In larger venous injuries, a 5-0 prolene suture (placed in eight-fashion) or vascular clips should be applied.

Intraoperative positioning of pulse oxymeter on the left great toe may be useful in case of protracted retraction of the vessels to avoid ischemic complications, especially in documented calcified iliac arteries.

Intraoperative arterial bleeding, a very rare complication, can be managed with direct suture repair.

Early postoperative vascular complications can be due to active bleeding, generally originating from inferior epigastric vessels injured by retractors during the exposure. Although superficial hematoma can be conservatively treated, a retroperitoneal hematoma should be carefully investigated with Computed tomography angiography (CTA) and CT scanning. Bleeding from arterial rectus sheath supply can occur in the early postoperative time (12-24 h). It is a rare but potentially life-threatening complication, presenting with abdominal or back pain, evidence of a palpable abdominal wall mass and symptoms and signs of hypovolemic shock.

Iliac or deep venous thrombosis (DVP) as well as arterial injuries are unusual (occur from 0.45% to 1%) and they are associated with prolonged vessels retraction or manipulation. Postoperative use of thrombosis prophylaxis agents (i.e Low-molecular-weight heparins LMWH) should be advocated in cases of thrombotic occlusion.

A ureteral injury during first exposure is uncommon but possible. Risk of venous and ureteral injuries increases in patients who underwent previous anterior retroperitoneal approach (22, 25). As the ureter may be encased in scar tissue, we place a ureteral stent in all our revision operations to prevent further injury.

A related complication in males is represented by RE. Symptoms duration could be transient or permanent with consequent impact on fertility rates (8). Surgical technique (blunt dissection; avoiding monopolar coagulation), and surgeon experience, may influence RE rate that ranges from 0% to 4.1% in retroperitoneal approach up to 13.3% in patients undergoing transperitoneal approach (8). Perivascular fibrous tissue containing the sympathetic fibers of the hypogastric plexus is adherent to the posterior surface of the

peritoneum and laying on the anterior surface of the lumbosacral spine. To complete disc exposure in L5-S1 sacral vessels should be ligated and coagulated with potential injury of IHP. To preserve the function of hypogastric plexus, the use of bipolar electrocautery is mandatory only on well identified small vessels to avoid electrical and/or thermal injuries. Despite these complications, innovative techniques have decreased the complications' rate; however, the potential surgical risks of anterior lumbar exposure require advanced technical skills (29). Thus, some authors recommended access surgeon assistance although to our knowledge, no consistent results are reported in the literature (25).

In our practice, orthopedic spine surgeons or neurosurgeons with expertise on anterior approaches perform the anterior exposure by themselves. According to other results in literature, we reported a low rate of perioperative access related complications (3.1%) (4, 5, 25,29).

Conclusions

ALIF advantages are well accepted and useful for degenerative disorders, spinal deformities and revision cases. Implantation of huge and lordotic cages improves fusion rate, thus restoring proper sagittal lumbar profile with preservation of the posterior muscles and bleeding reduction. Surgical time and recovery are faster. The related potential risks remain consistent without experience. The ability to manage surgical complications increases with experience. An adequate progressive learning curve may train spine surgeons to gradually and safely perform the exposure. Knowledge of abdominal and vascular anatomy is mandatory to prevent potential complications.

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Figures legend

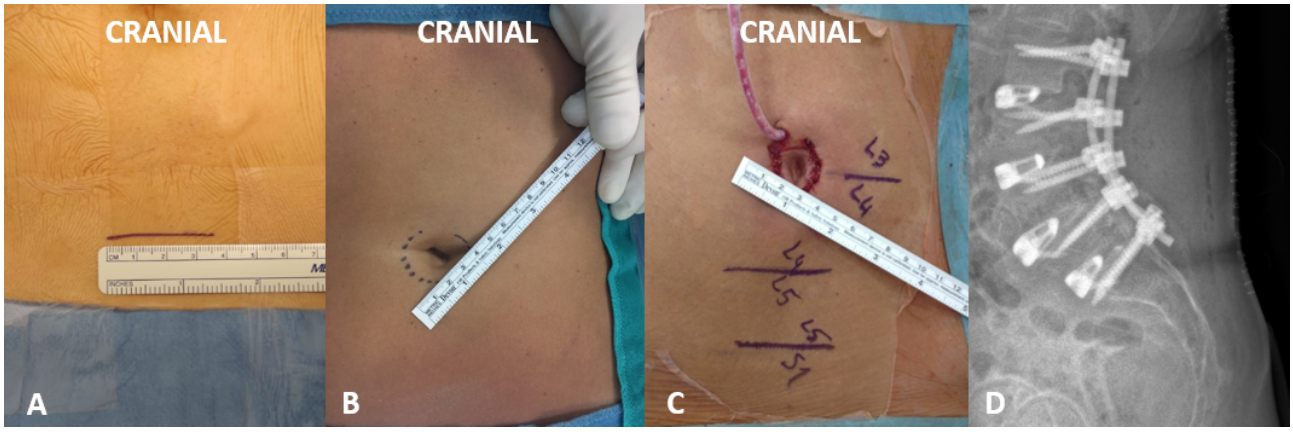

FIG 1) A. Standard mini-open skin incision B,C - Modified Perinavel 270° skin incision sec. Bassani used for multilevel disc approach D. Post-operative lateral X-Ray showing multilevel ALIF implant perfomerd with perinavel skin incision

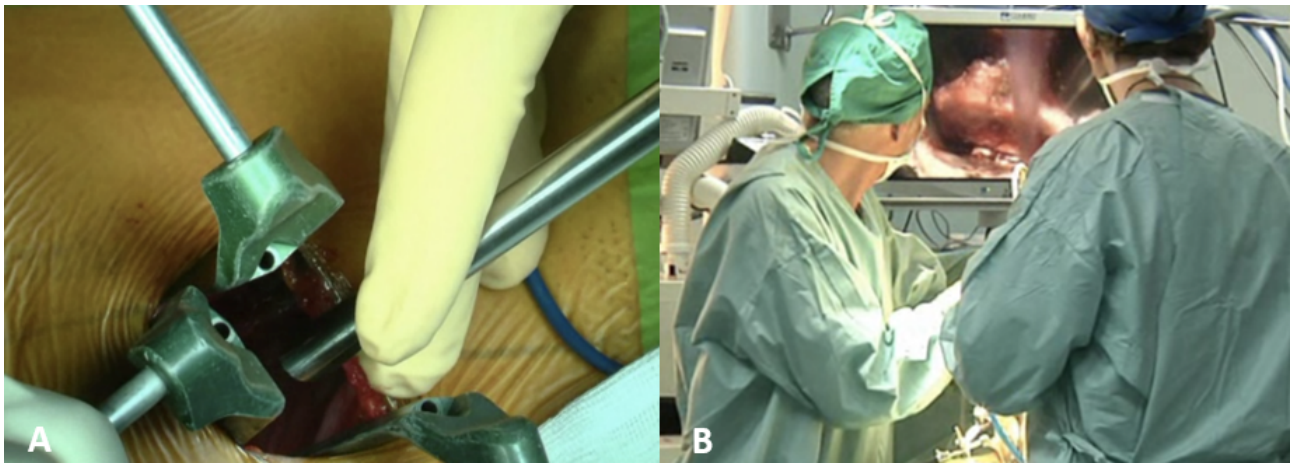

FIG 2) A. High Definition endoscopic assistance (30°) introduction B. Video-assisted ALIF procedure and operative theatre set-up.

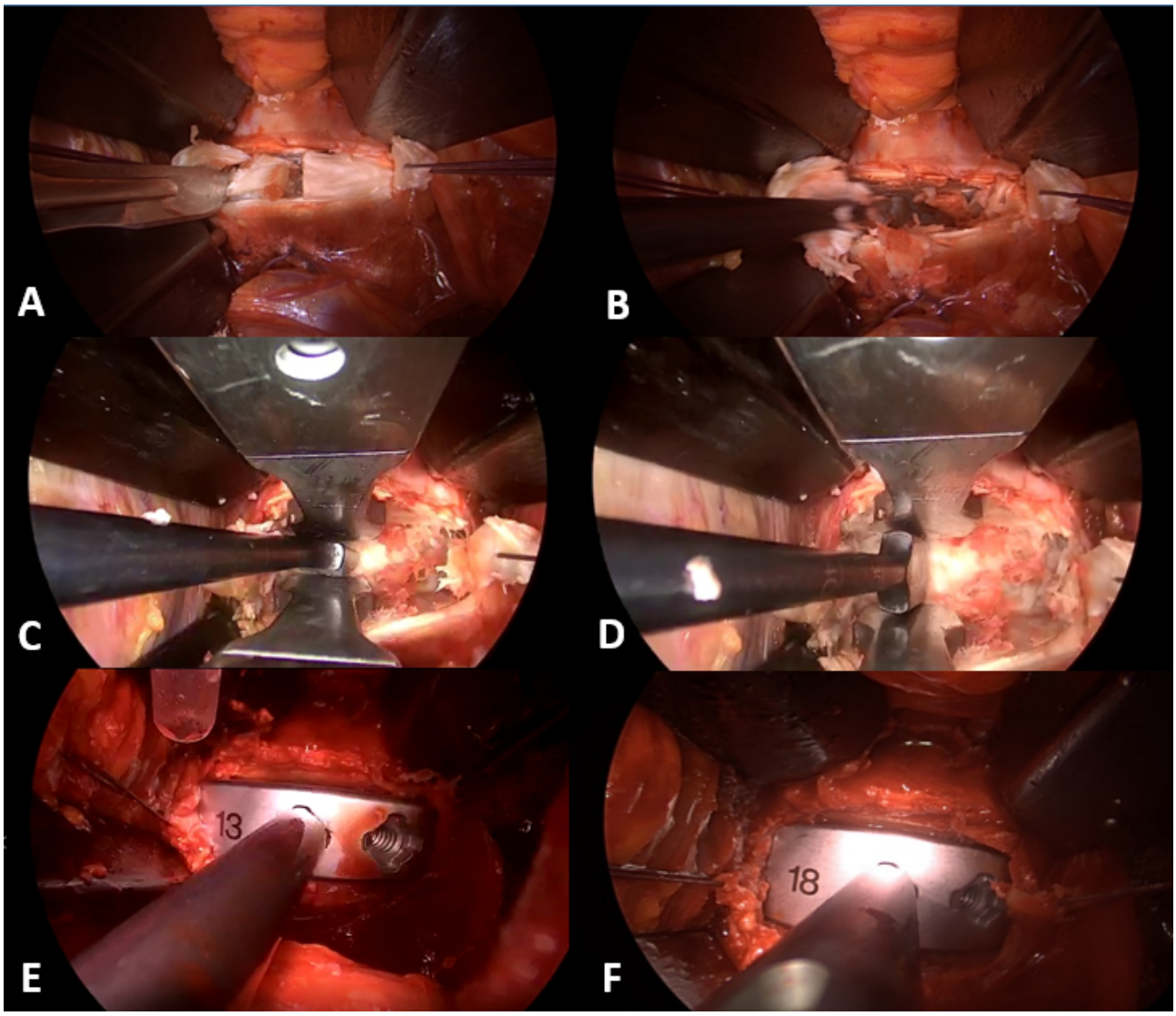

FIG 3) A. Intervertebral L5-S1 disc incision and «Window exposure» B. L5-S1 discectomy C-D. Opening of the disc space with spreader E.-F. Increased size templates implanted to find the proper fit.

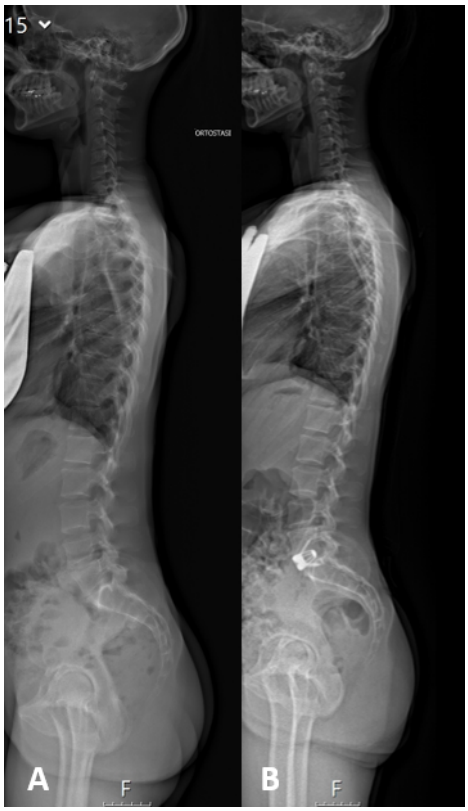

FIG 4) A. Pre and B. post-operative Full standing spine X-Rays-EOS of a L5-S1 ALIF with lordotic cage for treatment of DDD

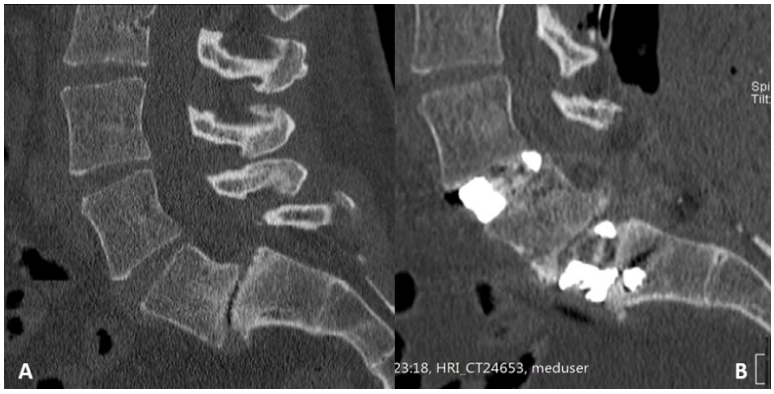

FIG 5) A. Pre and B. post-operative CT-Scan of a L4-L5-S1 ALIF for treatment of 2° Spondylolisthesis

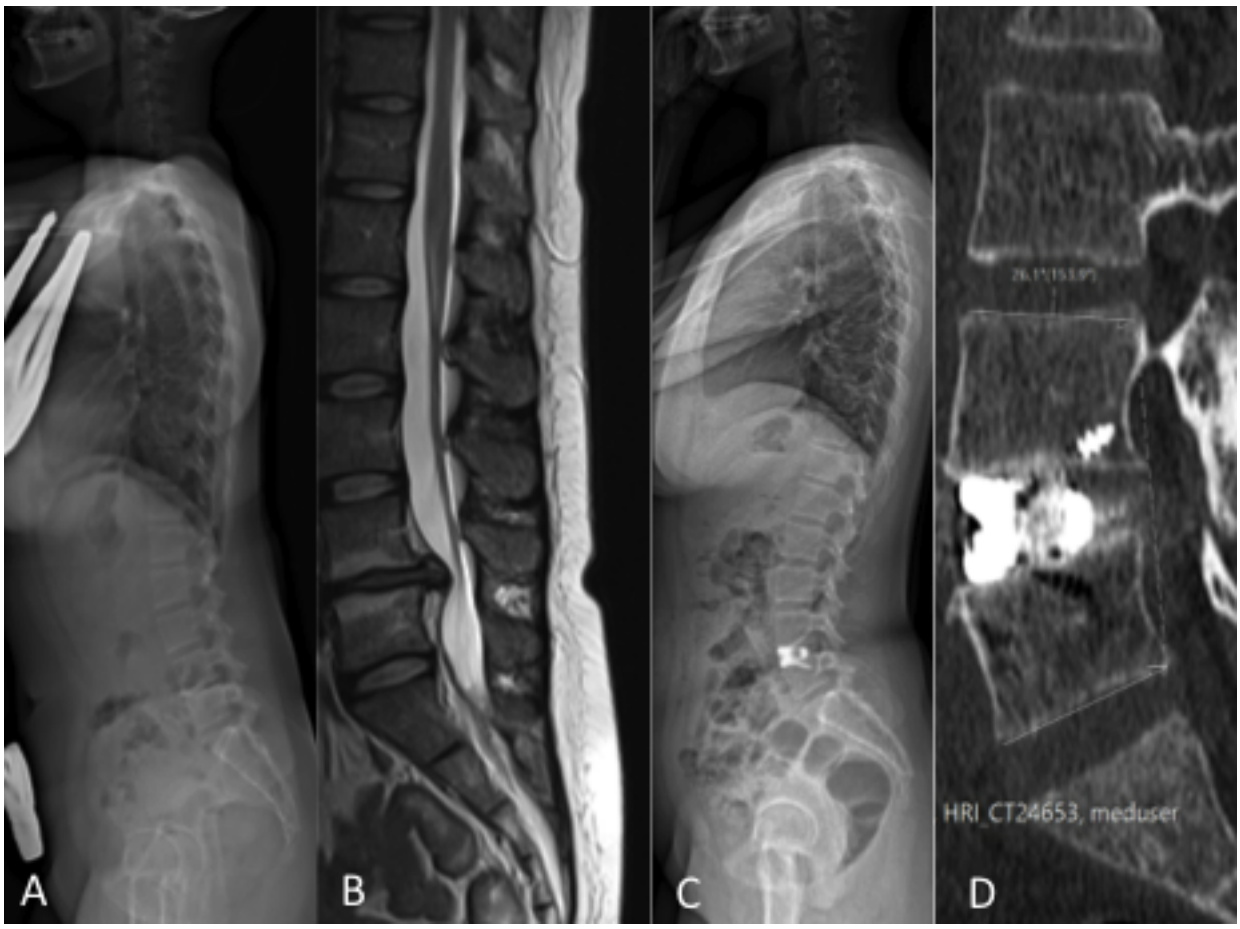

FIG 6) A. Pre-operative Full standing spine X-Rays-EOS showing sagittal imbalance and loss of lumbar lordosis with L4-L5 segmental Kyphosis. B. Preoperative sagittal T2 weighted image T2 showing L4-L5 discopathy (Pfirrmann 4) and disc herniation. C. Postoperative Full standing spine X-Rays-EOS showing L4-L5 ALIF with postoperative restoration of sagittal balance. D. Sagittal CT scan showing the correct positioning of the cage and L4-L5 segmental lordosis restoration.

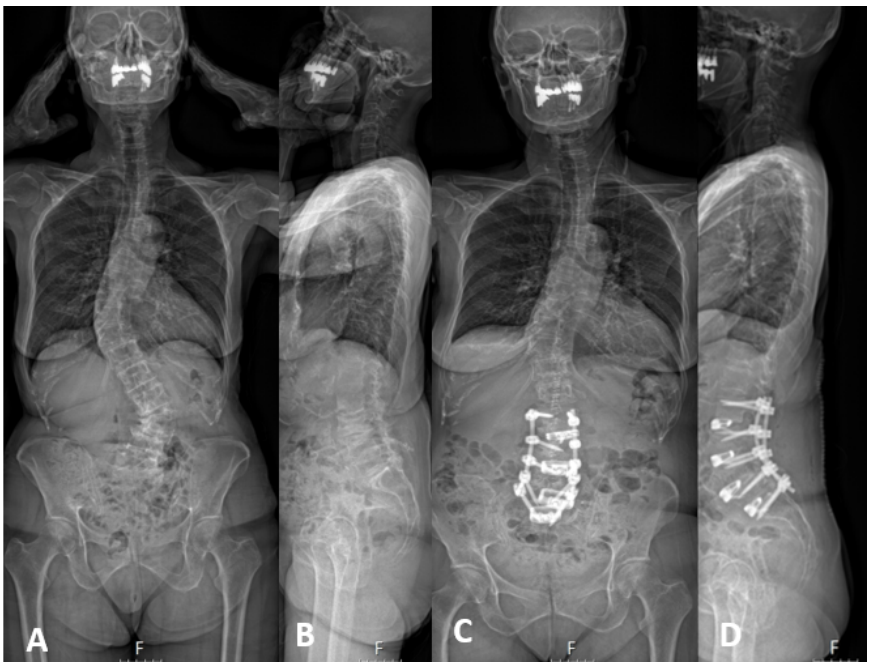

FIG 7) A. Pre and B. Post-operative Full standing spine X-Rays-EOS of a multilevel ALIF for treatment of adult deformity scoliosis.

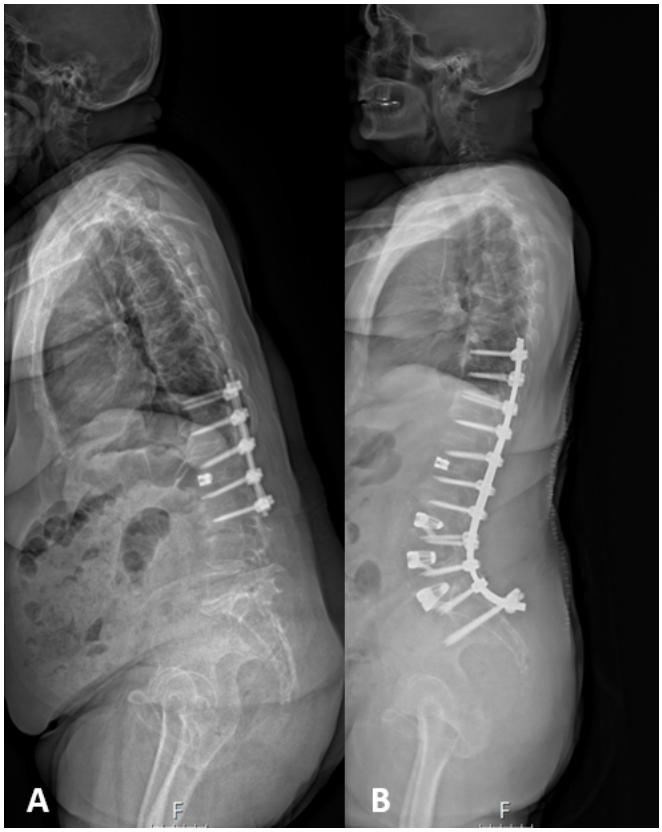

FIG 8) A. Pre and B. post-operative Full standing spine X-Rays-EOS of a multilevel ALIF for balance restoration in revision surgery

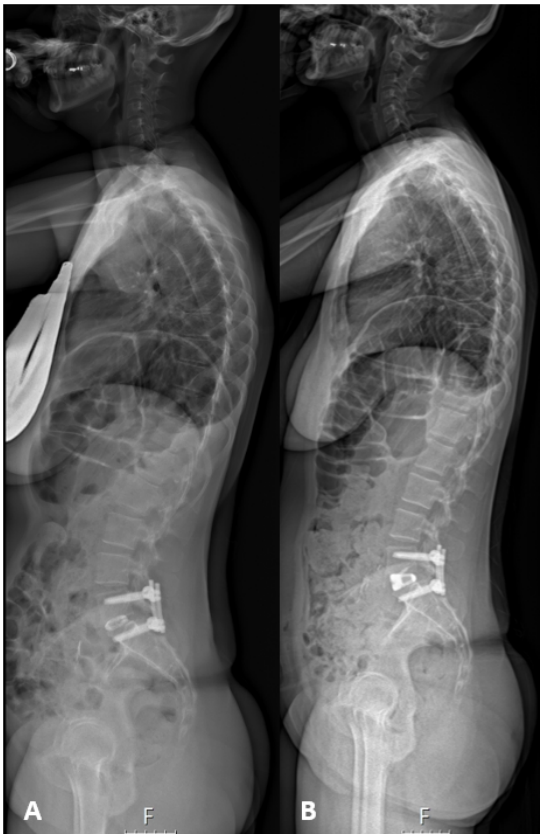

FIG 9) A. Pre and B. post-operative Full standing spine X-Rays-EOS of a L5-S1 ALIF for anterior cage removal and restoration of sagittal balance

1.6 Surgical and Radiologic Prognostic Factors in Intramedullary Spinal Cord Lesions

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Original article
World Neurosurg. 2021 Jun;150:e550-e560.

Abtsract

OBJECTIVE: The present study aimed to perform a comprehensive data analysis of 47 consecutive patients treated in 8 years and to observe how clinical, radiologic, and surgical factors affect early and long-term outcomes, recurrence rate, and survival.
METHODS: Clinical, radiologic, and surgical data were collected retrospectively from the review of a prospectively collected database. The neurologic disability was evaluated according to the modified Rankin Scale (mRS). Radiologic data were obtained by direct measurement performed on magnetic resonance imaging (MRI). Univariate and multivariate statistical analysis was performed.
RESULTS: From 2008 to 2016, 47 consecutive patients underwent microsurgical resection of intramedullary lesions (28 males and 19 females; mean age, 41.2 years). Ependymoma (53.2%), astrocytoma (14.9%), hemangioblastoma (14.9%), and cavernous angioma (6.4%) were the most frequent tumor histology. The mean follow-up duration was 69.3 months. Gross total tumor resection was performed in 80.8% of cases. Forty-two patients (89.4%) were alive at last follow-up. Five-year overall survival and recurrence-free survival were 92% and 82%, respectively.
CONCLUSIONS: Among the examined variables, age seemed to strongly correlate with outcomes; better chances of recovery and a good postoperative outcome were observed in younger patients. Surfacing lesions had a better early functional outcome than did intramedullary located lesions. Patients' preoperative neurologic and functional status

(mRS score ≥2) had a significant impact on late neurologic outcome. Progression-free survival correlated with the extent of tumor resection. Surgery should probably be performed before patients' neurologic decline, aiming to achieve maximal resection without compromising patients' quality of life.

Introduction

Intramedullary spinal cord tumors (IMSCTs) are rare neoplasms accounting for 4%e10% of all central nervous system tumors.1-3 The most frequent histologic types of IMSCTs are glial tumors (80%), such as low-grade astrocytomas (60%e70%) and ependymomas (30%e40%), whereas cavernous angiomas, lipomas, gangliogliomas, or secondary tumors are less frequent. The natural history of untreated tumors is characterized by progressive morbidity and mortality.4-7 The clinical features of each tumor are related to the growth rate, location, and longitudinal extent, and by the presence of associated syrinx.8-13 Clinical manifestations and radiologic features may contribute to the diagnosis. The most common clinical presentation is axial pain. Nerve roots are involved in cases of exophytic and laterally located tumor. Centrally located lesions can produce symptoms of myelopathy. Cranial nerve deficit is also a possible finding when the tumor involves the bulbomedullary junction. Severe spinal cord involvement can also cause respiratory, bowel, bladder, or sexual function impairment.9,12,14-17 Surgical resection is the treatment of choice for IMSCTs. Patients' clinical and functional outcomes may be influenced by several factors. The present retrospective study aimed to perform a comprehensive data analysis of 47 consecutive patients treated at our institution for IMSCTs over 8 years, to observe how clinical, radiologic, and surgical factors correlated with the early and longterm outcome, recurrence rate, and survival.

Methods

Between 2008 and 2016, 47 consecutive patients harboring IMSCTs were managed at the Department of Neurosurgery and Gamma Knife Radiosurgery of the San Raffaele University Hospital, Milan, Italy. Inclusion criteria were patients harboring an IMSCT or a tumorlike lesion surgically treated and a minimum follow-up of 1 year. Data were retrospectively analyzed by reviewing a prospectively collected database. Informed consent was obtained from all patients. Demographic data, medical history, duration of preoperative symptoms, functional status, and preoperative radiologic features were recorded. Intraoperative data, including surgical technique, intraoperative tumor findings (e.g., the intramedullary or surfacing location, and the absence of a favorable dissection

plane), the extent of resection, and type of dural closure (e.g., the direct suture or dural patch) were collected. Surfacing lesions were defined as eccentric tumors reaching the cord surface (Figure 1AeC); centromedullary lesions were defined as lesions located in the middle of the cord and surrounded by normal parenchyma (Figure 1DeF). Early and late clinical outcomes and surgical complications were also recorded. Early clinical outcome (including early complications) was defined as that assessed at hospital discharge or within 28 days after surgery; late clinical outcome was defined as that assessed at last followup evaluation. Late complications were defined as those found at follow-up later than 28 days after surgery. Mortality was defined as surgery related, if occurring within 28 days of surgery, or related to disease progression or not related to the disease. Tumor histology was determined by using the World Health Organization (WHO) grading system.18 Patients underwent clinical and radiologic follow-up by magnetic resonance imaging (MRI) every 3 months during the first year after surgery and every 6 months or more afterward, according to the histology of the tumor. The extent of surgical resection was evaluated at MRI performed 3 months after surgery. Gross total resection (GTR) was defined as a complete resection of all visible tumor. Subtotal resection (STR) was defined as a complete resection of the tumor mass with a small remnant still detectable on the postoperative MRI; biopsy was defined as <50% of tumor mass removal.19 Adjuvant radiation therapy and chemotherapy (CHT) were also recorded. Tumor recurrence was defined as regrowth of a GTR tumor or progression of an STR or a biopsied tumor, which underwent adjuvant radiation therapy. Further treatments for recurrences (reoperation, salvage radiation therapy, and CT) were also recorded.

Clinical Assessment

Preoperative, postoperative, and follow-up neurologic evaluations were analyzed, considering pain (axial and radicular), motor, sensory, bladder and bowel functions. Neurologic disability was evaluated according to the modified Rankin Scale (mRS),20 which classifies patients according to their functional status in 6 grades:

0: no symptoms at all

1: no significant disability despite symptoms; able to carry out all usual duties and activities

2: slight disability: unable to carry out all previous activity but able to look after own affairs without assistance

3: moderate disability: requiring some help but able to walk without assistance

4: moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance

5: severe disability; bedridden, incontinent, and requiring constant nursing care and attention

6: dead.

An mRS score 2 was referred to neurologically intact patients or those with some neurologic dysfunctions but independent in daily life, whereas an mRS score >2 defined a disabled patient, totally or partially dependent in daily life. The mRS together with the neurologic examinations and pain assessments were independently performed in person by at 2 authors with disagreement resolved by consensus.

Radiologic Evaluation

Radiologic data were obtained by direct measurements performed
on MRI studies imported in OsiriX Viewer (Pixmeo SARL, Geneva, Switzerland) (Figure 2). Tumor location, sagittal extension (Figure 2A), axial extension (Figure 2B), associated syringomyelia, and its extension (Figure 2C), presence of myelopathy, and tumor growth pattern were recorded for each patient. According to their location on MRI, tumors were defined as cervical, thoracic, and conus medullary located. Axial tumor extension was evaluated on the axial T1-weighted contrast-enhanced MRI slice, in which the tumor showed the maximum axial extension; the spinal cord area and the tumor area were measured and then the ratio between these 2 values was calculated (Figure 2B). The resulting value was reported in percentage and classified into 3 groups: group 1 <50%, group 2 50%e75%, and group 3 >75%. Craniocaudal tumor extension was evaluated on the sagittal T1-weighted gadolinium-enhanced MRI slice, in which the tumor showed the maximum craniocaudal extension, considering the number of metamers corresponding to tumor length (Figure 2A). Craniocaudal syrinx extension was evaluated on sagittal T2-weighted sequences (Figure 2C). Preoperative signs of myelopathy were defined according to the presence of an increased signal on T2-weighted sequences. The radiologic tumor growth pattern was classified as noninfiltrative (type A) and infiltrative pattern (type B).

Statistical Measurements

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, New York, USA). Statistical significance was defined as P0.05 (95% confidence interval). Distribution normality was assessed with the Kolmogorov-Smirnov test. We built multivariate logistic models taking each of the following as the dependent variables: early postoperative neurologic worsening, neurologic worsening at last follow-up, neurologic improvement at last follow-up, recurrence/progression of the residual tumor. Univariate variable selection was performed (taking P <0.10) with the Pearson c2 test for categorical variables and with the 2-sample t test or the Mann-Whitney U test (depending on the normality of the variable distribution) for continuous variables on the following variables: sex, age, duration of

preoperative symptoms/ signs, preoperative radiologic tumor location (cervical, thoracic, or conus), axial extension of the tumor, craniocaudal extension of tumor presence of syrinx and craniocaudal extension of a syrinx, preoperative signs of myelopathy, tumor growth pattern, myelotomy (performed or not), intraoperative tumor findings (intramedullary or surfacing tumors), cleavage plane (present or not), extent of resection (GTR, STR, or biopsy), histology, presence of postoperative residual tumor, preoperative mRS score (2 or >2), and preoperative disability (none, mild, moderate, or severe). In building the final model, $P < 0.05$ was considered statistically significant. The Kaplan-Meier product-limit method was used to analyze overall survival (OS) and progression-free survival (PFS). Time points were referred to as to the date of surgery. Cases were censored at the last available follow-up data. Univariate analysis was performed on the Kaplan-Meier curves using a logrank statistic, Breslow, and Tarone-Ware methods, to test how strong the association was among OS, PFS, and single variables. The log-rank method was selected to detect differences between the curves late in the time of the study; the Breslow test was performed to look for early differences, whereas Tarone-Ware was used as an intermediate strategy.

Results

Study Population and Preoperative Data

Twenty-eight patients (60%) were male and 19 (40%) were female, and the median age was 41.2 years (mean, 41 years; range, 5e75 years; standard deviation [SD], 0.7). According to the median age, patients were classified in 2 groups (group 1, <41 years and group 2, 41 years): 24 patients (51.1%) clustered in group 1 (4 of them were children) and 23 patients (48.9%) clustered in group 2. Genetic syndromes were detected in 4 patients: 3 patients were affected by Von Hipper-Lindau syndrome (VHL) and 1 by neurofibromatosis type 2. Preoperative symptoms are reported in Table 1. Eight patients (17%) presented with a single symptom, 33 (70%) with 2 symptoms, and 6 (13%) with 3 symptoms. Mean duration of preoperative symptoms was 291.7 days (range, 2e 1095 days; SD, 271.71). Symptoms lasted before surgery <3 months in 13 patients (28%), 3e12 months in 31 patients (66%), and >12 months in 3 patients (6%). Considering patients' preoperative functional status, 26 patients (55.3%) did not report any neurologic deficit negatively affecting functional independence (mRS score 1) and 21 (44.7%) showed some preoperative impairment of medullary functions; the median preoperative mRS score value was 2 (range, 1e5; SD, 1.4). Thirty-three patients (70.2%) were independent in daily life (mRS score 2), whereas 14 patients (29.8%) were partially or completely dependent. Tumors were located in the cervical area in 17 patients (36.1%), in the thoracic region in 14 patients (29.8%), and in the conus medullaris in 16

patients (34.1%). In 3 patients (6%), the tumor was located at the craniocervical junction, but they were considered in the data analysis as cervical cases. Axial tumor extension was calculated as <50% in 9 patients (19.2%), between 50% and 75% in 16 patients (34.0%), and >75% in 22 patients (46.8%). Mean craniocaudal tumor extension was 2.5 metamers (range, 1e8 metamers; SD, 2.1). Associated syringomyelia was identified in 12 patients (25.5%) and its mean extension was 1.9 metamers (range, 1e2 metamers; SD, 3.8). Myelopathy was detected in 28 cases (59.6%). According to the radiologic features of tumor growth pattern, type A accounted for 35 patients (74.5%) and type B accounted for 12 patients (25.5%).

Surgical Data

Somatosensory evoked potentials, motor evoked potentials, and D-wave intraoperative neurophysiologic monitoring (IONM) were adopted in all patients. All surgical procedures were performed by the senior author (P.M.). A posterior midline approach was performed in all patients. A standard laminectomy was performed in 33 patients (70%), and a laminoplasty in 14 patients (29.8%). Intraoperative ultrasonography was commonly used before dural opening, then before the myelotomy, and after tumor resection to detect a residual tumor. Surface located lesions numbered 26 (55.3%); intramedullary lesions numbered 21 (44.7%). After posterior midline durotomy and arachnoid dissection, a midline myelotomy was performed for the 21 intramedullary lesions. During tumor resection, a clear cleavage plane was found in 36 tumors (76.6%), whereas the remaining 11 (23.4%) showed an infiltrative pattern. Pial suturing was not performed in any patients. The dura mater was closed with a nylon monofilament running suture. Duraplasty was performed in 6 patients (12.8%).

Histology, Extent of Resection, Adjuvant Therapies, and Tumor Recurrence

Twenty-five patients (53.2%) harbored ependymomas: 15 (31.9%) were WHO grade II, 3 (6.4%) WHO grade III (anaplastic), and the myxopapillary subtype was found in 7 patients (14.9%). Seven patients (14.9%) harbored intramedullary astrocytomas: 3 (6%) of them were WHO grade I pilocytic astrocytomas, 3 (6%) were WHO grade II, and 1 (2.1%) was WHO grade III. In 7 patients (14.9%), the histologic diagnosis was hemangioblastoma and in 3 (6.4%), cavernous angioma. Five patients (10.6%) harbored other tumor types (miscellaneous), which consisted of 1 ganglioglioma, 1 intramedullary metastatic renal cell carcinoma, 1 intramedullary metastatic melanoma, 1 lipoma, and 1 hemangiopericytoma. GTR was performed in 38 patients (80.9%), STR in 7 (14.9%), and a biopsy in 2 (4.2%). GTR and STR were achieved in 21 (84%) and 4 patients with (16%) ependymoma, respectively. Among patients with astrocytoma, GTR was achieved in 5 (71.5%), whereas 2 underwent

biopsy (28.5%). In the hemangioblastoma group, GTR was achieved in 6 patients (85.7%) and STR was performed in 1 (14.3%). Regarding cavernous angiomas, GTR was performed in all patients. In the miscellaneous tumor group, GTR was obtained in 3 patients and STR in 2 (ganglioglioma and conocaudal lipoma). Fifteen patients (31.9%) received adjuvant treatments (Table 2). Among the GTR group (38 patients), 5 (13.2%) received adjuvant radiotherapy (RT), whereas 1 (2.6%) received RT plus CT. Among the STR group (7 patients), 3 (42.8%) received adjuvant RT and 4 received adjuvant RT-CT (57.14%). Among the biopsy group (2 patients), 1 received adjuvant RT and 1 adjuvant chemoradiotherapy. According to the tumor histology, adjuvant therapy was performed in 6 ependymomas (24%), 4 astrocytomas (57.1%), 2 hemangioblastomas (33.3%), 2 miscellaneous tumors, and 1 cavernous angioma in a patient with VHL.

Surgical Complications and Neurologic Outcome

Early complications were recorded in 5 patients (10.6%). Three (6.4%) required the early surgical evacuation of an acute hematoma and 2 (4.3%) required lumbar drainage positioning pseudomeningocele. No wound infections were recorded. The mean follow-up duration was 69.3 months. Late spine kyphotic deformity occurred in only 1 patient (2.1%). Figure 3A summarizes patients' neurologic symptoms and functional status according to mRS score, preoperatively, at hospital discharge, and at last follow-up; Figure 3B shows mRS score trend at follow-up.

Radiologic Follow-Up

During the follow-up period, 11 patients (23.4%) showed failure in tumor control, defined as either tumor recurrence after GTR (6 cases, 12.8%) or a progression of a postoperative residual tumor despite adjuvant therapies (5 cases, 10.6%). In 9 patients with high-grade astrocytoma (19.1%), 3-month postoperative MRI showed a residual tumor. At follow-up evaluation, tumor recurrence was observed in 6 patients after GTR (12.8%) and residual tumor progression was detected in 5 patients after STR (10.6%). Among the patients with ependymoma, 2 (8%) had recurrence and 2 (8%) experienced tumor progression. Among the astrocytoma group, 1 recurrence and 1 tumor progression were observed. For hemangioblastomas, 2 cases (8%) of tumor recurrence and 1 tumor progression were recorded. One case of cavernous angioma (VHL) recurrence and 1 case of ganglioglioma progression were observed. The overall mean time to progression or recurrence was 49.1 months (range, 12e96 months; SD, 38.11). The second surgery for residual progression or recurrence was performed in 7 patients (14.8%). Salvage RT was performed in 5 patients (10.6%), whereas 1 patient underwent salvage chemoradiotherapy. Postoperative residual

syringomyelia was detected in 7 patients (14.9%). Syrinx remained unchanged in 3 patients (6.3%), improved in 4 patients (8.5%), and completely recovered in 5 patients (10.6%). Radiologic evidence of cord tethering was detected in 1 patient (2.1%). Five patients died during follow-up: 3 (6.3%) as a result of disease progression and 2 because of unrelated medical conditions.

Results of univariate statistical analysis are reported in Table 3. At the multivariate statistical analysis in patients harboring intramedullary tumors, the postoperative worsening of mRS score was significantly higher than in those harboring tumors abutting the surface of the spinal cord. According to the Kaplan-Meyer analysis, the 2-year and 5-year predicted OS were 95% and 92%, respectively, whereas 2-year and 5-year PFS were 98% and 82%, respectively (Figure 4A and B). The extent of resection significantly correlated with the 5-year PFS at log-rank analysis (P ¼ 0.043). The 5-year predicted PFS for patients who underwent GTR, STR, and biopsy was 85%, 59%, and 50%, respectively (Figure 4C).

Discussion

IMSCTs are rare and can lead to progressive neurologic disability because of spinal cord compression or infiltration. Notwithstanding the advances in surgical technique and application of new technology, surgery of IMSCTs remains challenging and can be associated with a not negligible neurologic morbidity that may dramatically worsen patients' quality of life.21-25 Most series have reported a worsening of the preoperative status, pain, and dysesthesia development in about 20% of patients after surgical resection.7,17,26-28 Nevertheless, surgery remains the treatment of choice and may also influence positively the functional outcome and the PFS. Preoperative neurologic status, demographic data, and duration of symptoms seem to be the most important clinical variables influencing the neurologic outcome. In our series, the postoperative neurologic outcome showed a bimodal behavior (Figure 3B) characterized by early functional worsening (14 patients, 29.8%), followed by a progressive improvement (3/14, 6.4%), usually occurring within 6 months from surgery. By measuring the functional status score in the early postoperative period, 27 patients (57.5%) were neurologically intact, or with some neurologic dysfunctions not affecting the autonomy in daily activities (mRS score 2), whereas in 20 patients (42.5%), mRS score was 2. At the univariate statistical analysis, we found a strong correlation between early outcome and age: patients <40 years old showed a minor incidence of early postoperative deterioration. The mean and median age was lower (39.1 and 38 years, respectively) in those patients who did not deteriorate in mRS score after surgery if compared with those showing mRS score worsening (46.4 years and 54 years, respectively). According to Klekamp et al.,25 these data are related to the spinal cord

plasticity and a more vulnerable vascular supply of the cord given by the advancing age. The early postoperative worsening may depend on cord swelling secondary to surgical manipulation and older patients have less potential for compensating the microcirculatory instability.14,16,21-26,29-36 Moreover, a long history of symptoms may be explained by the presence of slow-growing and displacing tumors, which can often lead to vascular supply alteration or loss of spinal cord plasticity.37 Klekamp et al.25 reported that the permanent morbidity significantly correlated with the patient's preoperative status measured by mRS score or walking ability. According to these data, in our series, the persistence of neurologic deterioration at last follow-up was related to age (>40 years) and the presence of preoperative disability. In particular, we found that patients with an mRS score of 1 (P ¼ 0. 006) or mRS score 2 (P < 0.001) showed a better functional outcome at last follow-up. Based on the last available evaluation, 31 patients (66%) were independent in daily activities (mRS score2). Younger age (P ¼ 0.01) and absence of a preoperative disability (mRS score >2) (P ¼ 0.037) showed a statistical significance among those factors influencing clinical improvement at last follow-up. Considering these data, surgery should probably be proposed to the patient and performed before evidence of neurologic decline. Absence of preoperative disability may indicate absence of irreversible spinal cord impairment and younger people have a stronger ability to recover after transient neural damage. T2-weighted MRI can assess with reliable accuracy whether an infiltrating or displacing tumor can be expected. In this series, we found a correlation between the preoperative radiologic tumor features and the intraoperative findings. Type A and B tumors in our series account for 74.5% and 25.5% of cases and showed the presence or the lack of intraoperative distinct cleavage plane in 76.6% and 23.4%, respectively. In the present series, early neurologic deterioration was related to tumor cervical location (P ¼ 0.001), presence of preoperative myelopathy (P < 0.017), and a radiologic infiltrative tumor pattern (P < 0.019). Some investigators have reported early clinical worsening in patients harboring cervical tumors and in those with associated syringomyelia.12,25,38 In our cohort, we did not find any correlation between preoperative syrinx and early neurologic worsening; however, all the recorded cases of early postoperative functional deterioration were recorded in patients harboring cervical or thoracic IMSCTs. Furthermore, patients with cervical tumors presented a significantly worse early postoperative outcome than did those with a thoracic location (P ¼ 0.001). Preoperative signs of myelopathy also correlated with a worse early postoperative outcome.39,40 We did not find any significant correlation between axial and craniocaudal tumor extension and clinical outcomes. A statistical correlation between early postoperative deterioration and intramedullary located lesion (P ¼ 0.001) and myelotomy (P ¼ 0.002) was observed. Moreover, the intramedullary tumor location was found as the

sole independent factor in determining the early postoperative neurologic outcome. Figure 3B shows the mRS score trend after surgery, pointing out the more evident worsening of neurologic disability in centromedullary tumors in the early postoperative period compared with that observed in surfacing tumors. In both groups, subsequent neurologic improvement is noticeable; in surfacing tumors, the mean mRS score at last follow-up is similar or slightly better than that recorded preoperatively; in the intramedullary group, the mean mRS score recorded at last follow-up, notwithstanding the intercurrent improvement, remains worse than the preoperative score. Histology did not reach statistical significance on the postoperative outcome (P ¼ 0.067).25,35,41 Tumor pattern and intraoperative identification of the dissection plane are intuitively important factors in determining the risk of neurologic morbidity. However, we did not find any correlation between these 2 factors and patients' neurologic outcome. This finding can be explained with our strategy of avoiding excessive attempts of achieving GTR when a clear cleavage plane was absent. All surgeries reported in this study were performed under IONM and with intraoperative ultrasonography assistance.42,43 It has already been reported that the combined contemporary use of somatosensory evoked potentials, motor evoked potentials, and D-wave improves the overall sensitivity and specificity in predicting postoperative motor worsening.43-45 IONM monitoring has to be considered a further mandatory procedure adjunct to surgical resection.43-45 Intraoperative ultrasonography is helpful for adequate dural opening, tumor localization, and degree of resection.42,46 It allows the transitional zones between the tumor and the surrounding structures to be identified, defining the cleavage plane.42,46 Based on all these findings, whether a GTR is possible remains mainly an intraoperative decision. Centromedullary or posteriorly located lesions extending over multiple segments may disrupt the dorsal column tracts and may lead to a higher risk of postoperative neurologic worsening. The evidence of postoperative residual tumor (P ¼ 0.002) in cases of STR or biopsy, the extent of resection (P ¼ 0.039), the craniocaudal tumor extension (P ¼ 0.040), and the absence of cleavage plane (P ¼ 0.048) were all related to risk of recurrence. In type A tumors, the possibility of achieving a GTR was significantly higher than in type B tumors (P ¼ 0.04). In type A lesions, GTR was possible in 63.8% of patients, whereas in type B lesions, it was achievable in only 17% of patients. In the latter group, STR followed by adjuvant therapies is recommended. We recorded 6 cases of progressions at follow-up in patients who underwent GTR. Some investigators strongly suggested performing pial closure after tumor removal, because this maneuver seems to reduce incidence of arachnoid scar formation and postoperative tethering. 13,26 Our surgical strategy is not to perform any pial suture to avoid unnecessary spinal cord manipulation. Adopting this strategy, we did not record any case of spinal cord symptomatic adhesion.47

Moreover, we observed 9 cases (75%) of postoperative syrinx improvement. We did not find any correlation between the type of performed approach (laminectomy or laminoplasty) and the risk of late postoperative spine deformity. According to some investigators, laminoplasty can prevent or reduce the risk of postoperative kyphotic deformity by preserving the posterior tension band48; nevertheless, the only case of postoperative deformity in the present series was recorded in a young female patient undergoing a cervical laminoplasty for the removal of a bulbomedullary ependymoma. The patient presented with a kyphotic deformity of the cervical spine with C3-C4 subluxation 1 year after surgery and was treated by close reduction and anterior and posterior fixation, without any neurologic sequelae. According to the Kaplan-Meyer analysis, the predicted 5-year OS and PFS were 92% and 82%, respectively (Figure 3). At the statistical analysis, no correlations were found for the OS, probably because of the low number of disease-related deaths. Conversely, the extent of resection was found to significantly affect PFS (P ¼ 0.043) (Figure 4), confirming that GTR should always be attempted whenever achievable without endangering patients' quality of life.

Limitations of the Study

The retrospective design, together with the relatively limited number of cases, because of the rarity of the disease, which limit the possibility of obtaining significance at multivariate statistical analysis, may be the main limitations of this study.

Conclusions

Patient's age correlates with the surgical outcome: younger patients showed higher chances of recovery and better neurologic outcomes after surgery. Furthermore, preoperative neurologic and functional status (mRS score 2) significantly influenced the neurologic outcomes. Preoperative MRI signs of myelopathy correlated with a higher risk of early postoperative deterioration. Surfacing lesions have a more favorable early functional outcome than do intramedullary tumors. Considering these data, surgery should probably be performed before patients' neurologic decline. PFS correlates with the extent of tumor resection, confirming that GTR should always be attempted, without jeopardizing patients' quality of life.

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Figures

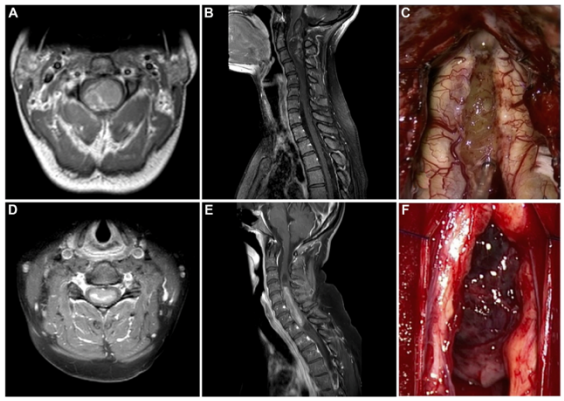

Figure 1. Sagittal (A) and axial (B) T1-weighted gadolinium-enhanced magnetic resonance imaging and intraoperative picture (C) of a surfacing tumor, defined as an intramedullary eccentric tumor reaching the cord surface; sagittal (D) and axial (E) T1-weighted gadolinium-enhanced magnetic resonance imaging and intraoperative picture (F) of a centromedullary tumor, defined as a tumor located in the middle of the cord and surrounded by normal parenchyma.

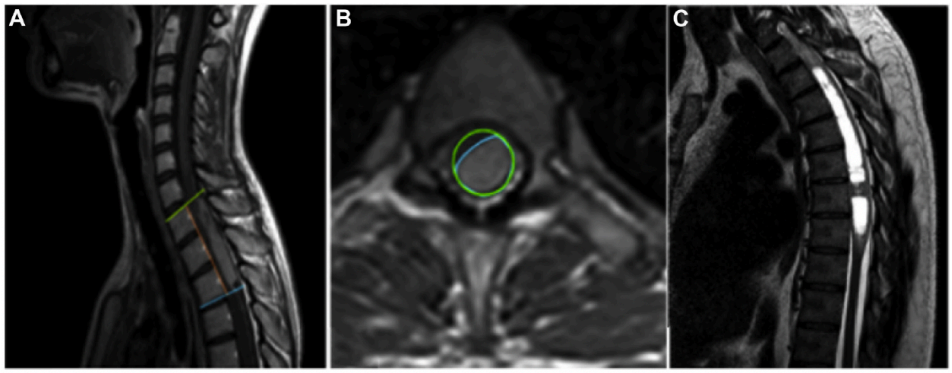

Figure 2. Magnetic resonance imaging (MRI) measurements. (A) Sagittal T1-weighted gadolinium-enhanced MRI used to measure the craniocaudal tumor extension (number of metamers). (B) Axial T1-weighted gadolinium-enhanced MRI slice in which the tumor presented the maximum axial extension. (C) Craniocaudal syrinx extension evaluated on sagittal T2-weighted MRI.

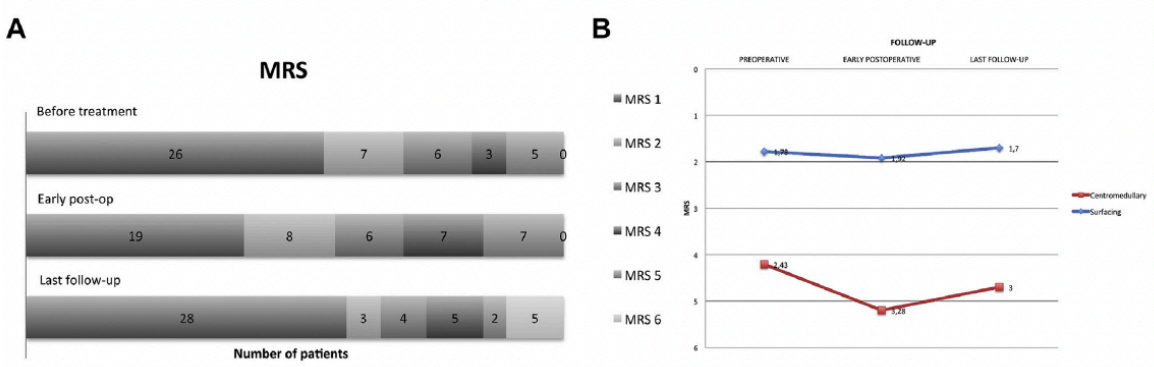

Figure 3. Modified Rankin Scale (mRS) score (A) before surgery, at hospital discharge and at last follow-up and (B) comparison of modified Rankin Scale score trend after surgery in surfacing and centromedullary tumors.

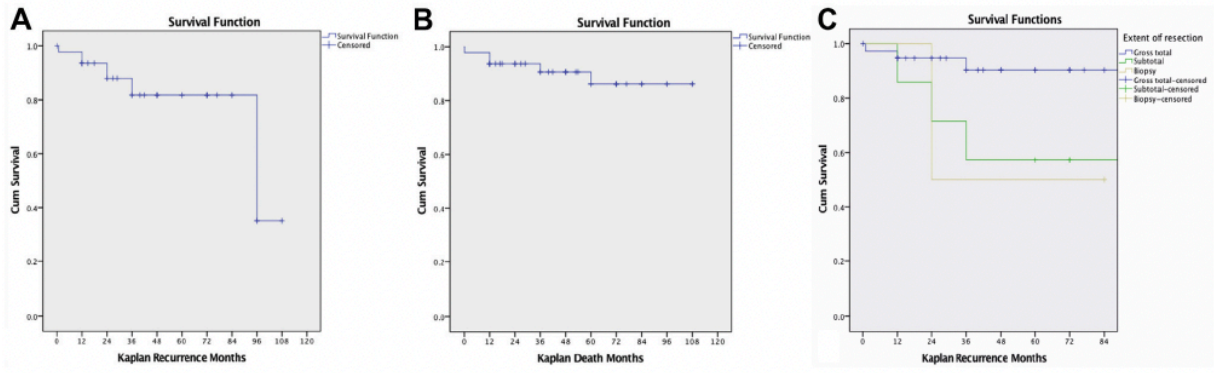

Figure 4. Kaplan-Meier survival analysis. (A) Progression-free survival; (B) overall survival; and (C) progression-free survival according to the extent of resection.

Tables:

	Number of Patients (%)						
	Preoperative	Early Postoperative	Last Follow-Up (Compared with Preoperative)				
Symptoms and Signs	Total Prevalence	Total Prevalence	Total Prevalence	Worsened	New Onset	Unchanged	Improved
Radicular pain	16 (34.04)	7 (14.8)	1 (2.1)	—	1 (2.1)	—	16 (34.04)
Axial pain	15 (31.9)	12 (25.5)	3 (6.3)	—	2 (4.2)	3 (6.3)	12 (25.5)
Sensory	32 (68.08)	24 (51.06)	8 (17.02)	3 (6.3)	2 (4.2)	5 (10.6)	24 (51.06)
Motor weakness	23 (48.9)	21 (44.6)	13 (27.6)	4 (8.5)	1 (2.1)	9 (19.1)	10 (21.2)
Bladder/bowel	6 (12.7)	6 (12.7)	6 (12.7)	—	—	6 (12.7)	—

Table 1. Summary of Preoperative, Early Postoperative, and Last Follow-Up Symptoms and Signs

Parameter (N = 47)	Gross Total Resection, n (%)	Subtotal Resection, n (%)	Biopsy, n (%)	Adjuvant Radiotherapy/ Chemotherapy, n (%)	Recurrence, n (%)	Progression, n (%)
Radiologic tumor pattern*						
Type A	30 (63.8)	5 (10.6)	—	8 (17.02)	5 (10.6)	2 (4.2)
Type B	8 (17.02)	2 (4.2)	2 (4.2)	7 (14.9)	1	3 (6.4)
Intraoperative tumor findings						
Surfacing	20 (42.5)	4 (8.5)	2 (4.2)	7 (14.9)	4 (8.5)	3 (6.4)
Centromedullary	18 (38.3)	3 (6.4)	—	8 (17.02)	2 (4.2)	2 (4.2)
Histology						
Ependymoma	21 (84)	4 (16)	—	6 (24)	2 (8)	2 (8)
Astrocytoma	5 (71.5)	—	2 (28.5)	4 (57.2)	1	1
Hemangioblastoma	6 (85.7)	1	—	2 (28.5)	2 (28.5)	1
Cavernous angioma	3 (100)	—	—	—	1 (33.3)	—
Metastasis	2 (100)	—	—	1 (50)	—	—
Ganglioglioma	—	1	—	1	—	1
Lipoma	—	1	—	—	—	—
Hemangiopericytoma	1	—	—	1	—	—
Total	38/47 (80.9)	7/47 (14.9)	2/47 (4.2)	15/47 (31.2)	6/47 (12.7)	5/47 (10.6)

*Type A, noninfiltrative; type B, infiltrative.

Table 2. Tumor Characteristics, Extent of Resection, Adjuvant Therapies, and Recurrences

Table 3. Results of Univariate Statistical Analysis

Variables	Early Postoperative Deterioration (%)	Deterioration at Last Follow-Up (%)	Improvement at Last Follow-Up (%)	Recurrence (%)
Age				
P	0.001	0.001	0.001	
≤40 years	13	0	100	—
>40 years	45.8	25	45.5	
Preoperative disability				
P		<0.001	0.037	
No disability	—	0	3.80	—
Mild		57.10	42.90	
Moderate		33.30	33.30	
Severe		0	12.5	
Preoperative independent				
P		0.006		
Independent	—	3.20	—	—
Disable (dependent)		31.30		
Tumor location				
P	0.001			
Cervical	58.80	—	—	—
Thoracic	28.60			
Lumbar	0			
Tumor pattern				
P	0.019			
Not infiltrating	21.60	—	—	—
Infiltrating	60			
Histology				
P	0.057*			
Ependymoma	28	—	—	—
Astrocytoma	71.10			
Hemangioblastoma	14.20			
Cavernous angioma	33.30			
Miscellaneous	0			
Craniocaudal tumor extension				
P				0.040
≤2 metamers	—	—	—	15.20
>2 metamers				42.90
Preoperative signs of myelopathy				
P	0.002			
No signs	10.50	—	—	—
Signs present	42.90			
Intraoperative tumor findings				
P	0.001			
Surfacing	11.50	—	—	—
Centromedullary	52.40			
Myelotomy				
P	0.002			
Not performed	11.50	—	—	—
Performed	52.40			
Cleavage plane				
P				0.048
Present	—	—	—	16.70
Absent				45.50
Extent of resection (surgeon's intraoperative perception)				
P				0.039
Gross total	—	—	—	15.70
Subtotal				57.10
Biopsy				50
Postoperative residual tumor (evidence on magnetic resonance imaging)				
P				0.002
Absent	—	—	—	13.90
Present				60.00

Statistically significant associations found between tumor/patient variables and radiologic/clinical outcome have been reported. Incidence of each outcome variable (column) among different groups (row) is shown (expressed as row percentage) when difference was statistically significant.
—Value not reported because it did not reach statistical significance.
*Value approaching without reaching statistical significance.

Table 3. Results of Univariate Statistical Analysis

CHAPTER 2

2.1 Introduction

Skull base lesions affect areas of the lower surface of the skull region. There are numerous and complex surgical approaches to the skull base. The concern of these challenging interventions is related to the potential problem of violating vital anatomical structures and the consequential impossibility to obtain a surgical radicality in some cases. Other potential problems concern the tricky reconstruction of the access area.

The management of these lesions requires the experience of different surgical disciplines to obtain the optimal result, a neurological surgeon, a head and neck surgeon or neuro-otologist, and plastic surgeon.

At the beginning of the history of skull base surgery the importance of an interdisciplinary approach was necessary to reduce the high morbidity and mortality rate. During the ensuing decade the management of these tumors has become less invasive than before with the morbidity and mortality rate gradually improving.

In the modern era a minimally invasive and interdisciplinary approach became increasingly more common, involving microvascular surgeons, neurosurgeons with appropriate competences of SRS, neuroradiologist and radiotherapist.

The evolution in treatment over the last century has ultimately led to an environment where functional outcome has taken precedence over disease eradication.

During the last years of my residency in neurosurgery I had the opportunity to deepen the knowledge of stereotactic radiosurgery with Gamma Knife (GK-SRS) for the treatment of some intracranial and skull base lesions.

Stereotactic radiosurgery (SRS) is a form of radiation therapy that focuses high-powered energy on a small area of the body.

Gamma Knife radiosurgery is a type of stereotactic radiosurgery, used to treat tumors, vascular malformations, and other abnormalities in the brain and skull.

Using specialized equipment to focus hundreds of tiny beams of radiation on a specific target with submillimeter accuracy, GK-SRS represent a real non-invasive out-patients method for treating brain diseases.

During my PhD I followed four studies concerning the different application of GK-SRS on different neurosurgical disease.

In this chapter I will present two of these four studies.

The first study with the title: “The emerging role of gamma knife radiosurgery in the management of glossopharyngeal neuralgia” published in the Neurosurgical Review

described the use of RSR to control pain in craniofacial pain syndromes. The study, a systematic literature, focused on the role of GK-SRS in the management of glossopharyngeal neuralgia was developed at the Gamma Knife Section of the Department of Neurosurgery and Radiosurgery Units San Raffaele University Health Institute of Milan.

Glossopharyngeal neuralgia is a rare but disabling craniofacial pain syndrome characterized by paroxysmal and usually unilateral pain attacks in the region of the ear, base of the tongue, tonsillar fossa and the angle of the jaw lasting from a few seconds to many minutes. Among treatment modalities such as medical therapy, microvascular decompression (in case of vascular nerve compression) or ablative therapies, the emerging role of Gamma Knife seems to be promising. Pain control and complication rates are better than those reported by other ablative procedures and microvascular decompression. Therefore, GK represent a valid minimally invasive option in the management of this neuralgia.

The second study with the title: "Multimodal Management of Metastatic Malignant Meningiomas: The Role of Radiosurgery in Long-Term Local Control" described the role of GK-SRS in the treatment of aggressive meningiomas. In the study two case examples were presented, which underlined the efficacy of therapeutical support and the less invasiveness of GK-SRS. The study was developed at the Gamma Knife Section of Department of Neurosurgery and Radiosurgery Units Humanitas research Hospital of Rozzano, Milan.

Malignant behavior of meningiomas rarely occur. Malignant meningiomas show aggressive behavior, like the invasiveness of venous sinuses, dura mater, bone and brain tissue, and a high risk of local recurrence and histologic malignant progression. In a few cases a systemic diffusion (extracranial malignant meningiomas) was reported. Therefore, a total body computed tomography scan as a standard extracranial examination should be performed in malignant meningioma, especially in long-term survivors. According to the higher rate of recurrence in malignant meningioma, a straight clinical and radiological follow-up, both cranial and extracranial is important to detect and treat any possible lesion in their earlier phases. Tumor subtotal surgical resection should be followed by adjuvant SRS even in patients with grade I primary lesion. In patients with grade II or III meningiomas, RT alone or in combination with surgery or chemotherapy should be performed at first recurrence. When local control is not reached, a multimodal approach should be performed. The role of the different RT modalities, such as SRS, has shown to be promising to achieve a better tumor control and a longer survival rate. Repeated GKRS control progression of the disease for several years with minimal collateral effects.

2.2 The emerging role of gamma knife radiosurgery in the management of glossopharyngeal neuralgia

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Neurosurg Rev. 2019 Mar;42(1):31-38

Abstract

Glossopharyngeal neuralgia (GPN) represents a rare craniofacial disorder accounting for about 1% of all craniofacial pain syndromes. GPN shares several pathophysiologic and clinical features with the more common trigeminal neuralgia. Medical therapy and microvascular decompression, in case of vascular nerve compression, represented the mainstay of GPN management. Other ablative therapies have been reported to date; however, few data are available because of the rarity of this pain syndrome. Among the ablative procedures, gamma knife radiosurgery (GKRS) has been recently introduced in the management of GPN with good pain control and low complication rates. Authors performed a systematic review of the published literature about GKRS in the management of GPN. Radiosurgical treatment data, pain control and recurrence rate have been analysed and compared. GKRS represented a valuable and effective treatment option for the management of GPN. Pain control and complication rates are better than those reported by other ablative procedures and microvascular decompression; however, future studies should be focused on the long-term efficacy of GKRS.

Introduction

Glossopharyngeal neuralgia (GPN) represents a rare craniofacial disorder accounting for about 1% of all craniofacial pain syndromes [2]. Its incidence is much more rare than trigeminal neuralgia (TN; 1%) [2]. Clinically, GPN is characterized by unilateral and strong

pain attacks located in the area of the base of the tongue, the posterior portion of the throat, the tonsillar fossa region and the angle of the jaw with irradiation on the deep portion of the ear canal [2, 22]. Pain is paroxysmal, lasting from seconds to few minutes, and may remit and relapse as for TN [2, 5, 22]. This area is innervated by both the XIth and the sensitive portion of the Xth cranial nerves, and according to this physio-anatomical data, some authors suggested the name vago-glossopharyngeal neuralgia [2, 4]. Triggering phenomena are swallowing, couching, chewing, speaking and yawing, and together with pain, sometimes GPN can be associated with cardiovascular manifestations, such as arrhythmias that can be potentially lethal [2, 16, 22]. The current diagnostic criteria for GPN according to the International Classification of Headache Disorders (ICHD, 3rd edition, 2013) are the following: (1) at least three pain attacks located in the abovementioned regions; (2) three or more of the following characteristics recurrent paroxysmal pain attacks lasting few seconds to 2 min—severe pain, shooting, stabbing of sharp pain—precipitated by swallowing, coughing, talking, or yawning; (3) no evidence of neurological deficits; and (4) pain syndrome not better accounted for another ICHD diagnosis [5]. In case of vagus nerve involvement, approximately 2% of cases, patients may also experience bradycardia, asystolia, syncope and seizures [20]. The most affected side in the left, with a left/right ratio of 3:2 [15]. GPN seems to share several features with the more common TN. It can be classified as idiopathic, in case of non-organic dysfunction or neurovascular conflict (NVC), causing nerve compression to the root entry zone (REZ) [2, 4, 9, 10, 20]. As for TN, the mechanism of pain is related to demyelination and re-myelination processes, of which vascular nerve compression is only sometimes responsible [3]. Medical therapy and microvascular decompression (MVD), in case of vascular nerve compression, represented the mainstay of GPN management [22]. To date, other ablative therapies have been reported; however, because of the rarity of this pain syndrome, few data are available. Among the ablative procedures, gamma knife radiosurgery (GKRS) has been recently introduced in the management of GPN with good pain control and low complication rates. The purpose of this study is to systematically review the available literature on GKRS for the management of GPN.

Material and methods

Search strategy

A systematic literature search was performed on Pubmed, Web of Science and Google Scholar by using the MeSHterms BGlossopharyngeal neuralgia, Radiosurgery, Gamma Knife, Stereotactic radiosurgery^. Eligibility and exclusion criteria Eligibility criteria were

English-language publications and studies reporting GKRS treatment. Exclusion criteria were no full-text documents, such as abstracts, no English language and no stereotactic radiosurgery or other radiation treatment.

Data selection and analysis

After initial screening by reviewing the full text articles, the selected publications were assessed for eligibility according to inclusion/exclusion criteria, and duplicated articles were excluded. Some additional studies were selected from articles and their references. By reviewing full text, three studies were excluded from the final analysis in order to avoid patients' duplication. Finally, the included papers underwent data extraction and analysis. Figure 1 summarizes the review process.

Evaluation criteria

Pain response to GKRS has been standardized according to the Barrow Neurological Institute Pain Intensity Score (BNI) [10]. BNI Grade I was defined as pain-free without medication; BNI Grade II as occasional pain but off medication, BNI Grade IIIa as no pain with continued use of medications, BNI Grade IIIb as occasional pain controlled with medication, BNI Grade IVas pain improved but not adequately controlled with medication and BNI Grade V as no pain relief [10]. Favourable outcome was considered in case of BNI between I and IIIb at last reported follow-up. Recurrence was defined as painful new event after a positive pain response to GKRS. Adverse reactions to GKRS were classified as any neurological change from the pre-treatment clinical status.

Statistical analysis

IBM SPSS Statistics for Mac, version 22.0.0 (IBM Corp., Armonk, N.Y., USA) was used for statistical analysis. Statistical significance was defined as $P = 0.05$. Categorical variables were compared with the two-sided Pearson $\chi 2$ test and Fisher's exact test.

Results

A total of eight studies were included in the analysis process. All the selected studies were retrospective case series. Three studied were excluded, because the same patients were added to a multicentre study [10, 19, 27, 29]. Table 1 summarizes the literature review. Patients' characteristics Forty-two patients undergoing GKRS for GPN have been reported between 2005 and 2016. The mean reported age was 62 years (median 62, range 36–99); among these, 17 were male (40.47%) and 25 were female (53.53%; male-to-female ratio 0.68). Data about the presence of NVC were reported in 30/36 cases: 24 patients presented NVC

(66.6%), while 12 cases had no NVC on imaging studies (33.4%). GKRS was performed after failure of previous medical therapy in 38/42 cases (90.5%); 1 patient (2.3%) underwent a nerve block procedure before GKRS; 4 patients underwent MVD (9.5%); 1 patient (2.3%) percutaneous rizothomy and 1 case (2.3%) balloon compression (Fig. 2).

Radiosurgical treatment

Two different targets have been considered for GKRS treatment. In 37/42 cases (88.1%), the distal portion of the glossopharyngeal nerve at the level of the glossopharyngeal meatus (GPM), whereas in 11.9% of cases (5/42), the cisternal part of the glossopharyngeal nerve (CIS) was targeted for the GKRS treatment. The mean reported maximal dose was 79.42 Gy (median 80, range 60–90). In almost all cases, the dose was administered by using a single shot with a 4-mm collimator.

Outcome results

Follow-up data were available in all cases [19]. The average follow-up period was 27 months (median 23.5 range 6–83). Outcome was reported for each single patient in 7/8 series (20 patients). At the last reported follow-up evaluation, patients were classified as BNI Grade I in 13 cases (65%), Grade IIIa in 4 cases (20%) and Grade V in 5 cases (15%). Additionally, Kano and colleagues in their series reported a favourable pain response (Grades I–III) in 16/22 cases (72.7%) and poor or no pain response (Grades IV–V) in 6/22 cases (27.3%) after GKRS. By applying this classification, the overall rate of favourable pain response was 78.6% (33/42), while poor response was reported in 21.4% of cases. By analysing pain response and NVC (n = 14), among those with NVC, 77.7% of cases good response and 22.3% of cases poor response; whereas among those without NVC, 80% experienced good pain response and one case (20%) showed poor response. Previous surgical treatments for GPN seemed not to influence response to GKRS, even if it is not possible to give definitive conclusions because of the few reported cases. By analysing pain response and target type, poor outcome was reported in 40% of CIS target, whereas 18.9% experienced poor response in the GPM target group. It has to be noticed that CIS target failure group was treated with a dose of 70 Gy, while in the remaining three cases of CIS target with good outcome, the adopted dose was ≥80 Gy ($\chi 2$ test $p = 0.174$). By comparing dose and pain response, poor outcome was reported in 50% of cases treated with a dose <80 Gy, while in 16.6% of those patients treated with a dose ≥80 Gy, experienced poor pain response ($\chi 2$ test $p = 0.065$;Fisher's exact test $p = 0.101$). Data on pain recurrence were available in 36 patients. Recurrence was reported in 15 cases (41.6%). A statistical significance was found between pain recurrence and target type

($\chi 2$ test $p < 0.001$); whereas, we did not find any statistical significance between pain response and target type ($\chi 2$ test $p = 0.281$). No adverse reactions were reported after single GKRS treatment. Two patients (4.7%) experienced hyperesthesia in the palatoglossal region after repeated GKRS for refractory pain, performed several months after the initial procedure [10].

Discussion

GPN is a rare craniofacial pain syndrome characterized by paroxysmal and usually unilateral pain attacks in the region of the ear, base of the tongue, tonsillar fossa and the angle of the jaw lasting from few second to any minutes [5, 14]. GPN shares some clinical features with the most common TN. Pain attacks are precipitated by some actions, such as swallowing or chewing; multiple attacks per day, up to 40, may jeopardize patients' quality of life [5]. The actual incidence of GPN is reported between 0.2 and 1.3% of all craniofacial pain disorders; however, the real incidence may be underestimated, because GPN is often misinterpreted or is not considered in the differential diagnosis of craniofacial pain syndromes [2, 14,20]. Some authors found a correlation between the nerve length and central myelin volume and the incidence of cranial neuralgias [4]. For glossopharyngeal and vagus nerves, authors reported a smaller length and volume if compared to the trigeminal nerve: this paradigm explained why GPN is less common than TN [4]. Similarly to TN, GPN can be classified as idiopathic cases, related or not to a vascular compression to the IXth–Xth nerve complex by the posterior-inferior cerebellar artery (PICA); otherwise, secondary cases caused by intracranial disorders (such as aneurysms, cerebellopontine angle lesions, persistent hypoglossal artery, petrositis) and extracranial diseases (oropharynx tumors, tonsillitis trauma, vertebral artery dissection and stylohyoid ligament ossification and elongated styloid process) and Chiari malformation [2, 4, 8, 14, 21–24]. According to these characteristics, an imaging study is mandatory in the management of patients experiencing GPN to differentiate idiopathic and secondary forms [22]. Magnetic resonance imaging and magnetic resonance angiography are indicated in order to visualize mass or vascular lesions, which may be responsible for GPN [2, 7, 22, 24]. Moreover, CT scans can help to visualize an ossified and elongated stylohyoid ligament, which can cause secondary GPN in the Eagle syndrome [1, 25]. Antiepileptic drugs, such as carbamazepine, represent the mainstay of GPN treatment; however, they can show some side effects or fail in controlling pain over time as in the experience of TN treatment [5, 20, 22]. In these cases, some other treatment options are available. MVD is considered in those cases related to PICA or other neurovascular compression [2, 22–24]. MVD represents a physiologic treatment option if compared to others ablative techniques, as reported in the management of TN, providing

pain relief in more than 90% of patients, with low recurrence rates [2, 22]. However, after MVD patients may experience partial or no pain relief, even if the rate of unsatisfactory surgical outcome is quite low [2]. Long-term failure rate of MVD ranged between 0 and 24% of cases; however, these data are not always reported in surgical series [2, 9, 15, 17]. In a recent series, long-term complete pain relief rate (>2 years) was of 94.4% [22]. MVD carried a risk of permanent cranial nerve deficits depending on the series, such as hearing loss, and the common complications of open surgical procedures [2, 22]. Together with MVD, intracranial or extracranial surgical section of the glossopharyngeal nerve has been proposed for the management of GPN [2]. These techniques, despite the high rates of short-term pain relief, are related to a high rate of recurrence and major complications [2, 22]. Another less common reported technique is the trigeminal tractotomy-nucleotomy [11, 22]. Despite this technique, provided quick pain control in almost all cases, less than 20 patients have been reported to date, and it is not possible to draw definitive conclusions on its efficacy and safety [22]. Additionally, percutaneous ablative techniques have been also applied for GPN [2]. Percutaneous radiofrequency thermocoagulation (PRT) is a well-known technique TN treatment [2]. Contrarily to TN experience, PRT for GPN is more difficult to perform, because the complex neurovascular anatomy is related to this region; the rate of damage to the adjacent vessels is high if compared to PRT for TN [2]. Despite the good outcome in terms of pain control, PTR presented a high risk of vocal cord paralysis and dysphagia meaning that it has to be considered only in very selected cases [2]. Among the ablative procedures, GKRS represents an emerging treatment option for GPN. GKRS is a well-known option in the management of TN with good outcome rates in terms of pain control and low complications [12, 18, 30]. GKRS has been introduced in the management of GPN in the 2005, and to date, a total of 42 patients have been reported [6, 10, 13, 15, 16, 28, 31, 32]. Pain control has been reported in the majority of cases, with a low complication rate (no complications after one treatment and 4% after a repeated GKRS) and a pain recurrence rate accounting for about 40%. Martinez-Alvarez and colleagues recently, reporting a concomitant case of TN and GPN both successfully treated by GKRS, stated that the two pain syndromes share a common pathophysiology, and therefore, response rates are comparable [15]. However, the interval between GKRS and pain response seemed to be shorter than TN, and these data may reflect the low number of GKRS cases or, in our opinion, the fact that by using similar doses of TN for GPN, the smaller size of the target may be responsible for this short interval [3, 4, 15, 32]. In most of the series, the GPM was targeted, while in only 11.9% of cases, the target was considered the CIS. Lévêque reported that the selection of the target was influenced by the radiation exposure of the brainstem, while other authors considered the GPM as the primary target of the radiosurgical treatment

[6, 10, 13, 15, 16, 19, 27, 29, 31, 32]. GPM can be well visualized by merging MR and CT imaging, and targeting the GPM seemed to be related to better outcome, allowing for a minor radiation exposure to the brain stem [10, 13, 16]. Moreover, the target has to include both the glossopharyngeal and vagal meatus, in order to improve the chances of a good pain response to GKRS [19, 32]. Previous surgical therapies did not influence pain response to GKRS for GPN, whereas these relationships in GKRS for TN are still controversial [12, 18, 26, 30]. As for TN, MVD for GPN is related to high pain control and low recurrence rates both at short- and long-term followup periods. At present, there is no consensus on the treatment dose for GPN [13]. Some authors stated that the treatment dose has to be ≥75 Gy, because it seems to be related to a higher rate of response and a longer pain-free interval [13, 15, 28]. Our review confirmed these data, showing that when the treatment dose is <80 Gy, one half of patients experienced a poor outcome, while this result decreased to less than 20% with a treatment dose ≥80 Gy. Additionally, these findings have been already reported in in the GKRS-TN literature, where the recommended dose ranges between 70 and 80 Gy [12, 18, 26, 30]. Martinez-Alvarez reported four cases treated with a dose of 90 Gy, with no side effects after a mean follow-up period of 33.75 months [15]. For TN, doses ≥90 Gy are occasionally related to a higher pain response; however, they are associated with a higher morbidity rate [12, 30]. For GKRS series, outcome data are not homogeneously reported, making it difficult to compare results from different series. By applying the same criteria for pain control, a favourable pain response has been reported in 78.6% of cases, and among these patients, recurrence has been reported in 41.6% of cases. One of the potential limitations of GKRS is the long-term pain control [12, 18, 26, 30]. In the largest series by Kano et al., pain recurrence was reported in the 50% of cases of patients experiencing a good pain response after GKRS treatment, after a mean follow-up of 45 months [10]. Stieber and colleagues stated that the suboptimal radiation of the entry zone in the jugular foramen was probably responsible for the pain recurrence 6 months after GKRS. In the remaining cases, recurrence has been reported from 2 to 24 months after GKRS. We found a statistical significance between pain recurrence and the type of target type while a trend toward significance between dose and pain response. Longer follow-up and larger cohort are needed to better outline the efficacy and safety of GKRS for GPN. The results in terms of pain control period are not comparable to the TN experience because of the few cases reported to date for GPN; however, the long-termefficacy of GKRS for pain control is a common issue with GKRS for TN [12, 18, 26, 30].

Conclusions

GKRS represents a valuable option for the management of GPN. Pain control and complication rates are better than those reported by other ablative procedures and MVD; however, the long-term efficacy of GKRS is not entirely defined. Further studies are needed to assess the optimal radiosurgical strategy and the long-term results.

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Figures

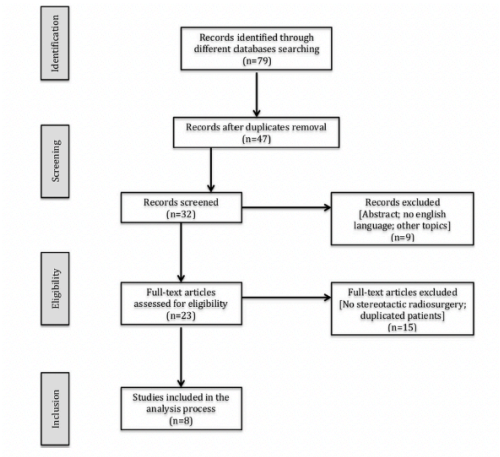

Fig. 1 Flowchart search results

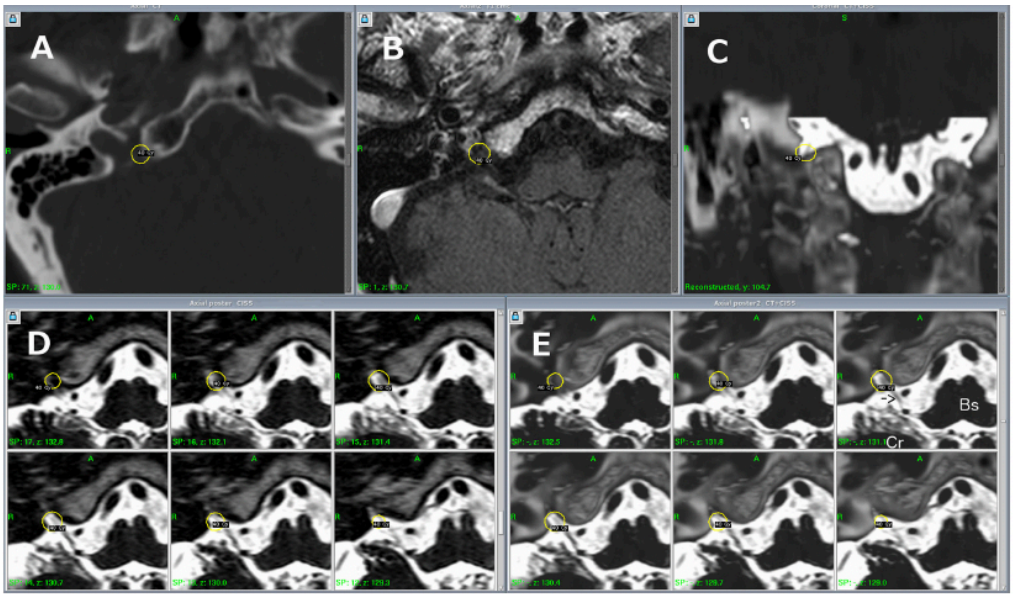

Fig. 2 GKRS treatment planning. Axial bone-windowed CT image showing the glossopharyngeal meatus (a). T1-weighted contrast enhanced MRI acquisition (b). Coronal three-dimensional constructive interference in steady-state (CISS) MRI merged with bone-windowed CT acquisition, showing the glossopharyngeal meatus (c). Axial CISS MRI, showing the treatment planning and the relevant dosimetry to the nerve (d). Axial CISS MRI merged with bone-windowed CT scan showing the relevant anatomy and the neurovascular conflict (black arrow) (e). Bs brainstem, Cr cerebellum

Table

Authors/year (*n*)	Age/sex	Side	Previous treatment	NVC	Target	Dose (Gy)	FU (months)	Outcome[a]	AE	PR	Notes
Stieber [28] (1)	N/A; F	R	MED	+	GPM	80	6	I	None	+	Pain-free 3 months; recurrence 6 months
Yomo [32] (2)	83; F	L	MED	+	GPM	60	50	I	None	+ (2 months)	New GKRS 7 months; 2 TC 10 and 10 months thereafter
	49; M	L	MED	−	GPM	75	12	I	None	−	−
Lévèque [13] (7)	83; F	N/A	MED	+	GPM	60	7	V	None	+	Repeated GKRS 7 months; TC 10 months
	62; M		MED	−	CIS	70	24	V	None	+	CS
	66; M		MED	+	CIS	70	24	V	None	+	MVD
	49; M		MED	−	GPM	75	32	I	None	−	−
	71; M		MED	+	GPM	80	13	IIIa	None	+	−
	36; F		MED	−	GPM	80	10	I	None	−	−
	65; M		MED	+	GPM	80	8	IIIa	None	+	−
O'Connor [16] (1)	99; F	L	MED	−	GPM	80	16	I	None	−	−
Martinez-Alvarez [15] (5)	56; F	N/A	MED	N/A	GPM	80	83	IIIa	None	−	PC 10 months
	73; F		MED; Rizo	N/A	GPM	90	71	I	None	−	PC 2 months
	62; F		MED; MVD	+	GPM	90	31	I	None	−	PC 6 months
	66; M		MED	N/A	GPM	90	19	I	None	−	PC 10 months
	37; F		MED; MVD	+	GPM	90	14	IIIa	None	−	PC 4 months
Heroux [6] (1)	43; M	L	MED	+	GPM	80	44	I	None	−	−
Xiong [31] (3)	88; F	R	MED	N/A	CIS	80	28	I	None	−	PI 2 days
	51; F	L	MED	N/A	CIS	80	25	I	None	−	PI 7 days
	56; M	R	MED	N/A	CIS	86	23	I	None	−	PI 11 days
Kano [10][b] (22)	60[c]; 8; M 14; F	15L 7 R	2 MVD; 1 BC; 18 MED; 1 NB	15/22	GPM	80[c]	45[c]	16 I–III; 6 IV–V	2/22[e]	8[d]	5 new SRS; 2 MVD; 2 NS

NVC neurovascular conflict, *FU* follow-up, *PR* pain recurrence, *F* female, *M* male, *mos* months, *N/A* not available, *L* left side, *R* right side, *GKRS* gamma knife radiosurgery, *MED* medical therapy, *Rizo* percutaneous rizothomy, *BC* balloon compression, *NB* nerve block, *CIS* cisternal nerve portion, *GPM* glossopharyngeal meatus, *TC* thermocoagulation, *CS* cortical stimulation, *PC* pain control after, *PI* pain improvement after, *NS* nerve section, *SRS* stereotactic radiosurgery

[a] According to the Barrow Neurological Institute Pain Score

[b] 22 patients

[c] Median values

[d] Among 16 patients BNI I–III

[e] 2 hyperesthesia in the palatoglossal region after repeated GKRS

Table 1 Literature review of published series of GKRS for GPN

2.3 Multimodal Management of Metastatic Malignant Meningiomas: The Role of Radiosurgery in Long-Term Local Control

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Original article

World Neurosurg. 2019 Aug; 128:562-572.

Abstract

BACKGROUND: Metastatic meningiomas (MMs) are rare (0.1 of 100 cases). Their treatment requires a multimodal approach, with surgery, radiotherapy, chemotherapy, and radiosurgery, which allows a long-term local control (LC) and an extension of free survival. In this study, the authors performed a review of the literature and reported 2 cases of patients affected by extracranial MMs, with long-term follow-up.

CASE DESCRIPTION: Case 1: A 48-year-old woman was admitted for resec- tion of an extra-axial falx lesion (meningioma G1). After 2 years, the lesion got a local recurrence, resected with a histologic diagnosis of meningioma G3. During the next 9 years, the patient underwent 5 Gamma Knife radiosurgery (GKRS) procedures for local recurrence. At 56 years, she was readmitted for a surgical local recurrence (histologic definition: anaplastic meningioma G3). At the age of 62, the patient underwent a right lobectomy for a lung mass (histologic diagnosis: anaplastic meningioma G3). After that, multiple lesions at soma L5 and adrenal gland were discovered and then monitored. Case 2: A 48-year-old woman was operated for a lesion involving torcular herophili (meningioma G2). After 3 years, a local recurrence requires GKRS combined with tamoxifen. In the next 7 years, she underwent 5 GKRS procedures for local recurrence. The patient also underwent chemotherapy with octreotide. At the age of 61, she discovered multiple lesions in both lungs, liver, and kidney.

A hepatic biopsy showed anaplastic meningioma G3. Also this patient does not suffer from any neurologic or clinical deficits.
CONCLUSIONS: LC in malignant meningioma is achievable through a multi- modal approach; GKRS makes possible LC, but a novel aspect of these lesions is opened to discussion: the metastases. These reports show that multimodal treatment for MMs is an effective approach with good LC and improvement of overall survival. However, a long survival may allow systemic diffusion of the disease, in particular, when sagittal sinus is involved.

Introduction

Meningiomas are one of the most common slow-growing benign tumors of the central nervous system representing between 20% and 35% of primary brain tumors in adulthood.1 For what regard their classification, the World Health Organization (WHO) recognize 3 different categories of meningiomas, according to the presence and the number of mitotic figures or expression of hypercellularity, cell change, necrosis, loss of pattern of growth, and cell pleomorphism. Most of these lesions belong to WHO grade I group, also known as common meningioma, which do not present any sign of malignancy; however, the WHO classification also recognize the so-called atypical (grade II WHO) and anaplastic meningioma (grade III WHO), which instead show sign of aggressiveness. Malignant meningiomas represent approximately 20%e 35% of all meningiomas.2,3. These show aggressive behavior, like the invasiveness of venous sinuses, dura mater, bone and brain tissue, and a high risk of local recurrence and histologic malignant progression.4,5 Among malignant meningiomas, there are few cases showing systemic diffusion (extracranial malignant meningiomas) that occur in less than 0.1 of 100 cases.6 Several structures can be infiltrated, such as lungs, which are also the most affected organs (37%), but also bones (16.5%), spine (15.2%), liver (9.2%), and other structures such adrenal glands or neck, which altogether account for 21.9%.1-6

It is known that such invasive, recur- rent, and malignant meningiomas often require adjuvant therapy after surgery, which consists in a combination of radiotherapy (RT), chemotherapy, and radiosurgery. This multimodal approach should allow us to achieve long-term local control (LC) and with a secondary positive effect on progression-free survival (PFS).

In this study, the authors performed a review of the literature and reported exemplificative cases. Two patients with long-term follow-up (15 years) affected by meningiomas infiltrating dural sinuses are reported. The patients were treated with a combination of surgery, RT, chemo- therapy, and radiosurgery with Gamma Knife (GK), achieving long-

term LC. These patients after several years of follow-up showed secondary systemic diffusion with thoracic and abdominal metastatic lesions. We conclude that with a strict monitoring of the tumor and a multimodal approach, it is possible to achieve a long-term LC with a positive impact on patients' survival.

Patients and methods

We report 2 patients treated for malignant meningioma with the involvement of the dural sinuses. Multimodal management to achieve LC was required. However, after several years of LC, metastatic spreading of primary meningioma occurred.

Case 1

A frontal parasagittal meningioma infiltrating the sagittal sinus was partially resected in a 48-year-old woman (Simpson grade IV). The first histologic diagnosis was meningothelial meningioma (WHO grade I). After 2 years of follow-up, the patient underwent a second surgery for local recurrence. The second histologic diagnosis was anaplastic meningioma (WHO grade III) with high cellularity, frequent mitosis (16 10 high power fields), high nuclear pleo- morphism, necrotic areas, and Vimentin expression. In the next 9 years, the patient underwent 5 Gamma Knife radiosurgery (GKRS) procedures and a third surgery for a local recurrence (histologically diagnosed as WHO grade III). A dose of 15 Gy (50% isodose) was delivered to the tumor in each repeated GKRS treatment. At the age of 62, the patient presented with 3 lesions: one at the level of the vertebral body of L5, one at the level of the right adrenal gland, and one in the right lung, for which she underwent a right lobectomy and mediastinum lymphadenectomy. The lung lesion was histologically defined as an anaplastic meningioma metastasis (grade III).

At the present day, after 3 years of follow-up, the patient is in good clinical conditions (Karnofsky performance scale 100) (Figures 1 and 2).

Case 2

A 47-year-old woman with atypical meningioma (WHO grade II) involving the torcular was surgically resected (Simpson grade IV). After 3 years, the patient showed a local recurrence that required a stereotactic radiation treatment (32 Gy in total) combined with tamoxifen. From the age of 54 to 61 years, the patient underwent 5 GKRS procedures for local recurrences,

adjacent to the previously irradiated field (dose range, 15e16 Gy, 50% isodose). Furthermore, the patient was treated with octreotide with no evident benefit. At the age of 61, multiple bilateral lesions in the

lungs, liver, and kidney arose. A liver biopsy showed an anaplastic meningioma (grade III). This patient nowadays is in good neurologic conditions with KPS 100. No recurrent brain lesions have been showed at the last follow-up, which happens at the age of 63 years (Figures 3 and 4).

Literature review

A literature review of the current clinical data was performed searching on a scientific literature database such as MEDLINE and Scopus. Relevant references of published articles were screened to in- crease the scientific quality of paper. The keywords searched were MMs, local recurrence, atypical meningiomas, malig- nant meningioma, and extracranial metastasis.

From 1960 to 2018, a total of 130 studies were included (123 case reports, 6 case re- ports with literature review, and 1 editorial article), summarized in Table 1.Full-text English articles containing the search key- words indicated above were included. The most useful keyword combinations were "atypical meningiomas AND metastatic meningioma" and "malignant meningiomas AND metastatic meningiomas." Case series, case reports, and literature review of distant metastases in meningiomas were included. Our review includes cases of primary intracranial meningioma with secondary spreading and cases of primary MMs with intracranial lesions. A recent systematic review of the literature was performed by Surov et al.6 From their analysis, they included 115 cases with 164 metastatic lesions from 1990 to 2012.6 As can be seen in Table 2, a total of 168 cases were collected in our review (80 patients were male, 85 were female, and in 3 patients, sex data were not reported). The average age was 55.7 years (range, 8e100 years; standard deviation [SD] 17.2 years). According to WHO classification, primary tumors were in 40.5% grade I (meningothelial, papillary, psammomatous, fibroblastic, or transitional), 31.5% grade II (atypical), and 22.1% were grade III (anaplastic). In 5.9% of the cases, however, the grade was not reported. In 31% of the reported cases, the type of resection was classified as Simpson grade IV. In 22% of cases, a dural sinus was involved at the time of first surgical resection. In a small percentage of cases (6%), metastases were identified simultaneously or even before primary tumors. The mean number of surgeries for patient has been reported to be 2.65 (range, 1e7; SD 1.75). In 18.5%, histologic tumor progression was observed in subsequent surgeries. Adjuvant RT was reported in 27.4% of cases. Radiosurgery was performed in 4% of cases. The median time of metastatic spreading was 5.6 years (range from 6 months before intracranial diagnosis to 22 years after first surgical resection; SD 5.8). In the 168 reported patients, a total of 220 distant metastases were recorded. Meningioma metastases were localized predominantly in the lung (48.1%) and were represented by a single lesion in 23.1% or multiple lesions with or without pleural involved in 25%, which are reported in

Table 3. The spine was involved in 18.7% of the reported cases, the skeletal bone in 11.4% of cases, and the liver in 9.5%. Subcutaneous tissue of posterior neck, lymph nodes, and parotid glands was involved in 6.3% of cases. Other rare locations such as mediastinal, abdominal, and pelvic lymph nodes, diaphragm, retroperitoneal space, skin, spleen, or adrenal gland represented 5.9% of all metastatic lesions. In 57.3% of the cases, the metastatic spreading involved only a single anatomical site, whereas in 42.7% of the cases, the metastatic spreading involved 2 or more organs. Adjuvant chemotherapy was reported to be used only in 10% of cases (18 patients). The mean follow-up was not specified in the majority of the cases, but it is included between few months and 15 years after tumor systemic dissemination. The mortality rate was 19.6% at 5 years after metastatic spreading.

Discussion

Malignant Meningiomas The treatment of meningiomas depends on histology and localization of the lesion. Surgical management with gross total resection represents the treatment of choice. Malignant meningioma management may be challenging due to aggressive behavior and high rate of local recurrence, and surgery alone is often ineffective to achieve LC and long-term survival. A multimodal management is therefore recommended. It is known that the correlation between histology and recurrence rate and that the different types of treatment may influence recurrence rate and PFS.60-64 According to different studies, WHO grade I meningiomas treated by surgery alone have a recurrence rate that ranges from 0% (at 32.5 months' follow-up) to 22.5% (mean recurrence of 26.2 months).60,61 Atypical (grade II) and anaplastic meningiomas (grade III) instead have a recurrence rate respectively of 38% and 78% (mean recurrence >5 years) after surgery alone; this is the reason why a more strict follow-up and the use of adjuvant treatment should be proposed for such malignant lesions.62,63 The use of adjuvant therapies in malignant meningiomas should be more intense in case of residues; it has been shown in fact that rates of recurrence change in a significant way in case of gross total resection (between 9% and 50%) or a subtotal resection (between 36% and 83%).2 RT, including a single session of stereotactic radiosurgery (SRS), hypofractionated stereotactic RT, and other RT modalities, is commonly used for residual meningiomas. Malignant meningiomas treated with surgery followed by RT showed a PFS of 85% at 2 years or 62% at 3 years, thus demonstrating the need of alternative or adjunctive therapies beyond surgery.64 RT is most commonly used as an adjuvant therapy in case of STR to avoid recurrences, especially in high-grade tumors. However, even with the use of RT after surgery, recurrence rate for malignant meningiomas remains high (>65%).65,66 The role of SRS for these aggressive tumors has demonstrated to be extremely useful in controlling such lesions, partly because patients treated with

adjuvant therapy receive additional cranial imaging and are diagnosed with recurrence earlier than patients only undergoing resection.67 In order to be able to specifically address SRS, additional molecular studies of these tumors may help stratify patients whose tumor biology predisposes them to recurrence or predicts radiosensitivity. More specific studies should be performed to define the "perfect" dosage; different studies show in fact that the LC rates at 5 years with SRS using a margin dose higher than 13 Gy range between 16% and 32.1%.68,69 The 3- and 5-year overall survival for patients with WHO grade II were 97.1% and 88.3%, respectively, compared with 66.7% and 66.7% for patients with WHO grade III meningiomas. 69 Mathiesen et al70 reported their follow-up data of 100 consecutive patients submitted to surgery for parasagittal meningiomas involving venous sinuses, showing that patients with Simpson grade I presented a recurrence rate of 10%, whereas in Simpson grade IV, there was a recurrence rate of 72%. The same study70 demonstrated that the combined treatment of direct GKRS, after a tailored microsurgical resection (Simpson grade IV and GK), achieved a low recurrence rate of 10%, similar to Simpson grade I results. In this series, the tumor proliferation indices (MIB-1/Ki-67) were prognostically relevant for recurrence after either microsurgery or GKRS. Therefore, they concluded that tumor proliferation indices are correlated with recurrence after microsurgery and radiosurgery, in other words, useful adjunct but only in patients with tumors of low proliferative index. At last, the authors also suggested that GK should probably be used as part of the initial surgical management. Even though the use of GK radiosurgery seems to have improved in a long-term follow-up, they pointed out that recurrence and malignancy remained a problem, which is not always solved by repeated radiosurgery. Chemotherapy may be an option in case of refractory and high-grade meningiomas or for the treatment of multiple metastatic sites; however, at present, there are no relevant and effective drugs for this condition.

Cytotoxic agents, somatostatin analogues, and targeted therapy have been evaluated in meningiomas. As with mesenchymal tumors, the treatment should include anthracyclines and alkylating agents.71 Even though the understanding of meningioma cell biology has progressed recently to develop combination therapies that act in multiple pathways, the complex and biological aggressiveness makes the malignant meningioma resistant to the drugs as shown in the case series presented by Kanthan and Senger.71

Systemic Diffusion

Although meningiomas rarely spread, the risk of systemic metastases is correlated with histologic aggressiveness.71 If all the meningiomas are considered, the general prevalence of metastases is around 0.76%.26 According to the literature, metastases may be detected in several structures, such as the lungs (48.1%), the spine (18.7%), the skeletal bone (11.4%),

and the liver (9.5%). Subcutaneous tissue of posterior neck, lymph nodes, and parotid glands instead are involved in 6.3% of the cases. Mediastinal, abdominal and pelvic lymph nodes, diaphragm, retroperitoneal space, skin, spleen, or adrenal gland represented 5.9% of all metastatic lesions. Other locations are even rarer. According to a recent study,71 in 57.3% of the cases, the metastatic spreading involves a single anatomical site, whereas in 42.7%, more than 2 organs were involved.6,71 The location of meningioma metastases depends mainly on the route of dissemination. Four different routes of dissemination have been proposed: (1) via the jugular vein (supported by evidence of metastatic disease in cervical lymph node, thyroid, lung/pleura), (2) via the paravertebral venous plexus ("Batson's venous plexus drainage") as (3) it connects with the vena cava (according to abdominal localization) or (4) via lymphatic and cerebrospinal fluid way.71 There are no definitive criteria to predict the ability of meningioma to spread, and histologic grade seems to be the most important predictor of recurrence or metastatization. 4 Most patients with distant metastases have a history of repeated surgical resection of the primary tumor, suggesting a role for the grade of surgical resection in the spreading.6,26,71,72 Simpson grade for resection has been demonstrated to influence the recurrence rate of meningiomas both after surgery and radiosurgery.26 Clear risk factors for the development of metastases from a meningioma include histologic criteria such as high cellularity, cellular heterogeneity, high mitotic rate, nuclear pleomorphism, tumor necrosis, and invasion of adjacent blood vessels.6,71,73 The main route of spreading is hematogenous. The invasion of adjacent venous sinuses or plexus may represent a possible associated risk factor both for local recurrence and spreading. Therefore, parasagittal, paratorcular, and falcine meningiomas may give rise to metastases more frequently.71,74-77 In the review of Surov et al,6 dural sinus was involved in 22% of cases. Even if an association between local recurrence, dural venous sinus invasion, and malignant histologic grading has been reported, no risk factors have been demonstrated to cause metastatic spreading.6 They also found that 31.3% of MMs were clinically silent, concluding that the prevalence of metastases in meningioma may be underreported.6 The mean time between first surgery and systemic spreading ranges between 6 months and 20 years. Concurrent (<6 months) or synchronous metastases rarely occur.6,71 To date, there is no standard treatment of MM. According to the higher rate of recurrence in malignant meningioma, the authors encourage a straight clinical and radiological follow-up, both cranial and extracranial, to detect and treat any possible lesion in their earlier phases. It is the opinion of the authors that an STR should be followed by adjuvant SRS even in patients with grade I primary lesion. According to the literature,3 in patients with grade II or III meningiomas, RT alone or in combination with surgery or chemotherapy should be performed at first recurrence. When LC is not reached, a

multimodal approach should be performed. The role of the different RT modalities, such as SRS, has shown to be promising to achieve a better tumor control and a longer survival rate. More than 30 years ago, Taylor et al 78 presented a historical series, consisting of 132 patients treated for intracranial meningiomas. The actuarial LC rates at 10 years for the 3 treatment groups were as follows: subtotal excision alone (18%); subtotal excision plus postoperative radiation therapy (82%); and total excision alone (77%). The actuarial determinate survival rates at 10 years were 49%, 81%, and 93%, respectively. Postoperative radiation therapy was also effective for patients treated at the time of the first recurrence, with an actuarial LC rate at 10 years after salvage treatment of 30% for patients treated with surgery alone and 89% for patients receiving postoperative radiation therapy at the time of salvage.78 More recently, Kokubo et al79 published a series of 20 patients with a recurrent meningioma, where they reported a general LC rate at 5 years of 36% (41% for benign meningiomas and 30% for atypical or malignant meningiomas); the 5-year survival rate instead was of 47%. No serious complications of RT were observed in any of the patients. However, higher doses of radiation, using sophisticated radiation techniques, may be necessary to obtain higher control rates. An important study has also been published by Hardesty et al67 with their big series about atypical meningiomas treated with adjuvant SRS; their analysis suggested that in case of aggressive lesions, such as atypical meningiomas, a close observation should be always considered. They, in fact, noted that although postoperative adjuvant SRS did not significantly affect tumor recurrence rates, a longer followup may reveal a therapeutic benefit.67 We support the idea that a continuous tumor monitoring is determinant of outcome. In case of evidence of tumor progression or recurrence, an SRS or resurgery should be performed. In our patients, this strategy has been very useful in long-term LC but probably has favored the systemic spread of the disease.

Conclusions

Malignant meningiomas are typically associated with poorer survival and higher rates of recurrence. When complete removal is not possible, a close follow-up after the initial combination of surgery RT or radiosurgery should be performed. In the cases presented, when meningiomas further recurred, repeated GKRS was performed, and it was possible to control progression of the disease for several years with minimal collateral effects. Histology, number of previous resection, and invasion of dural sinuses could have been prognostic factors to systemic diffusion, as further demonstrated in the literature and in the 2 reported cases. Therefore, we can conclude that long-term follow-up of patients with relapsing or aggressive meningiomas will show systemic spreading through metastatization, especially to lungs or bones. We recommend total body computed

tomography scan as a standard extracranial examination in malignant meningioma long survivors. To further evaluate the effectiveness of the therapeutic strategies chosen, novel chemotherapy or radiation therapy regimens should be explored minutely.

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Figures

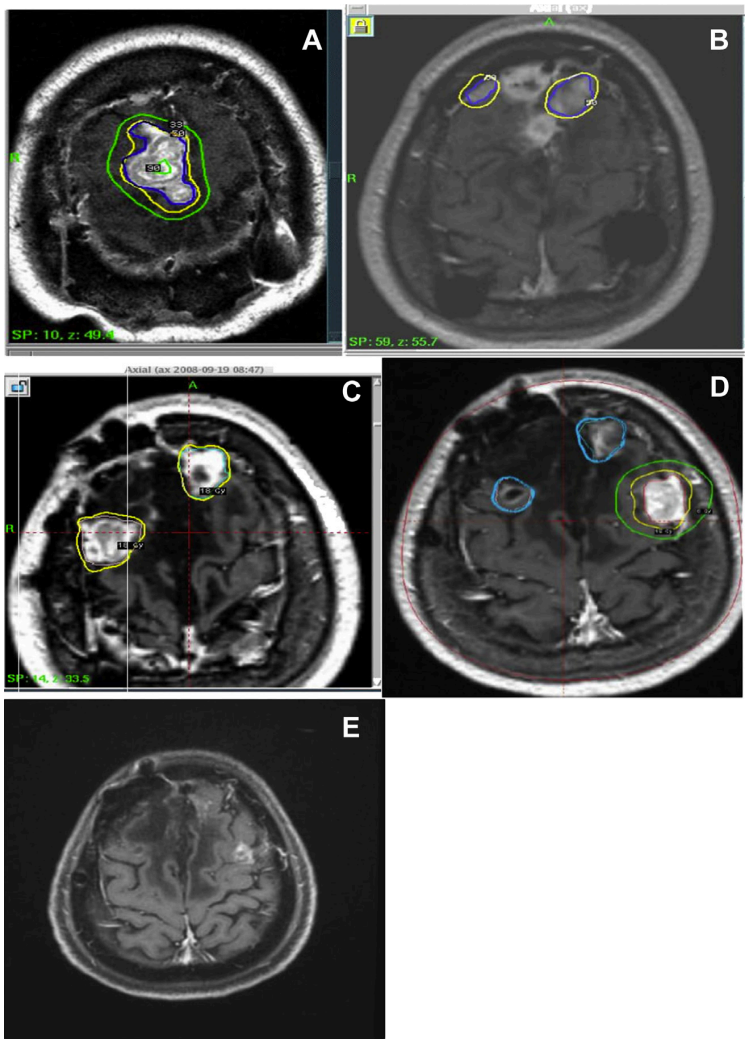


Figure 1. Evolution through the years of the metastases in patient 1 (AeE). Local recurrence after surgery: anaplastic G3. Five Gamma Knife radiosurgery procedures and a new surgery for local recurrences (G3 World Health Organization). In every occasion a dose of 15 Gy (50% isodose) was delivered to the growing tumor.

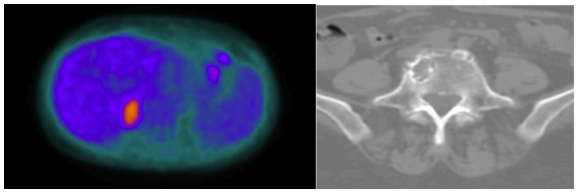


Figure 2. Lung and spine metastasis: meningioma anaplastic G3.

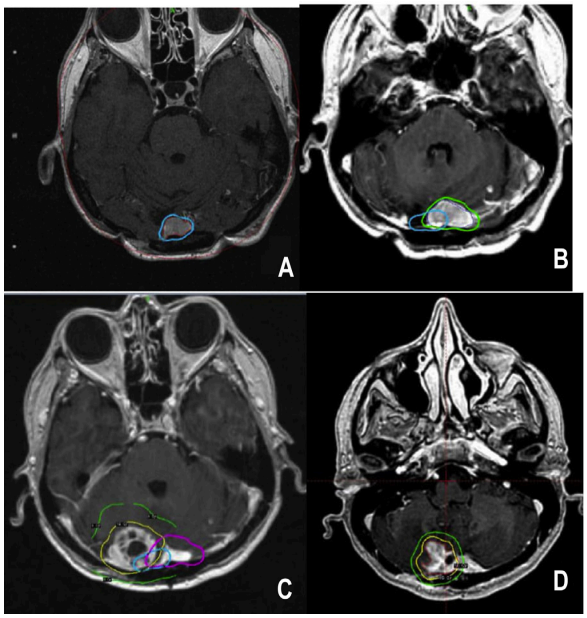


Figure 3. Evolution of brain metastases in patient 2 (AeD). Five Gamma Knife radiosurgery procedures for local recurrences in contiguous fields (dose range, 15e16 Gy; 50% isodose). It is important to note that the recurrence was not in the field of previous radiosurgical treatment.

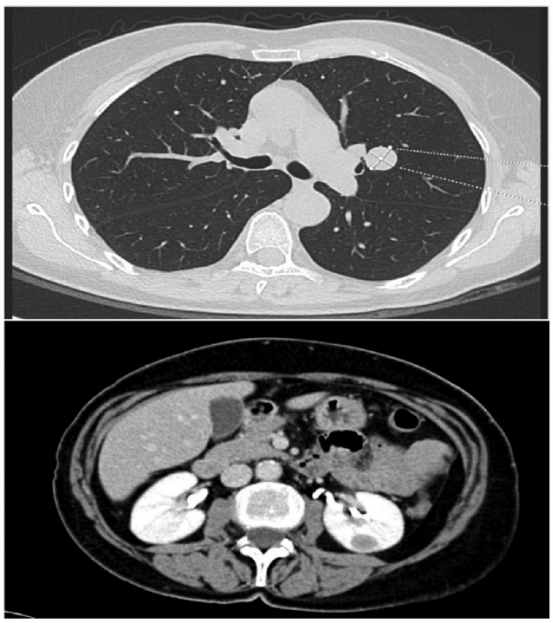


Figure 4. Lung kidney and liver metastasis: the biopsy for lung metastasis showed anaplastic meningioma G3.

Tables

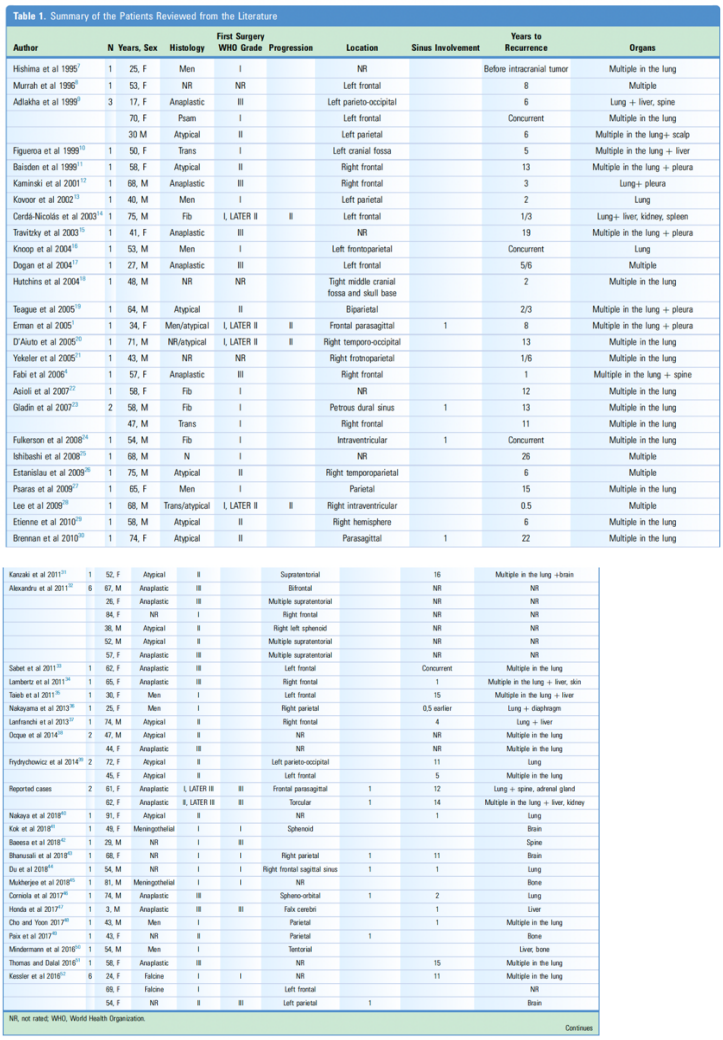


Table 1. Summary of the Patients Reviewed from the Literature

Author	N	Years, Sex	Histology	First Surgery WHO Grade	Progression	Location	Sinus Involvement	Years to Recurrence	Organs
Hishima et al 1995[7]	1	25, F	Men	I		NR		Before intracranial tumor	Multiple in the lung
Murrah et al 1996[8]	1	53, F	NR	NR		Left frontal		8	Multiple
Adlakha et al 1999[9]	3	17, F	Anaplastic	III		Left parieto-occipital		6	Lung + liver, spine
		70, F	Psam	I		Left frontal		Concurrent	Multiple in the lung
		30 M	Atypical	II		Left parietal		6	Multiple in the lung+ scalp
Figueroa et al 1999[10]	1	50, F	Trans	I		Left cranial fossa		5	Multiple in the lung + liver
Baisden et al 1999[11]	1	58, F	Atypical	II		Right frontal		13	Multiple in the lung + pleura
Kaminski et al 2001[12]	1	68, M	Anaplastic	III		Right frontal		3	Lung+ pleura
Kovoor et al 2002[13]	1	40, M	Men	I		Left parietal		2	Lung
Cerdá-Nicolás et al 2003[14]	1	75, M	Fib	I, LATER II	II	Left frontal		1/3	Lung+ liver, kidney, spleen
Travitzky et al 2003[15]	1	41, F	Anaplastic	III		NR		19	Multiple in the lung + pleura
Knoop et al 2004[16]	1	53, M	Men	I		Left frontoparietal		Concurrent	Lung
Dogan et al 2004[17]	1	27, M	Anaplastic	III		Left frontal		5/6	Multiple
Hutchins et al 2004[18]	1	48, M	NR	NR		Tight middle cranial fossa and skull base		2	Multiple in the lung
Teague et al 2005[19]	1	64, M	Atypical	II		Biparietal		2/3	Multiple in the lung + pleura
Erman et al 2005[1]	1	34, F	Men/atypical	I, LATER II	II	Frontal parasagittal	1	8	Multiple in the lung + pleura
D'Aiuto et al 2005[20]	1	71, M	NR/atypical	I, LATER II	II	Right temporo-occipital		13	Multiple in the lung
Yekeler et al 2005[21]	1	43, M	NR	NR		Right frotnoparietal		1/6	Multiple in the lung
Fabi et al 2006[4]	1	57, F	Anaplastic	III		Right frontal		1	Multiple in the lung + spine
Asioli et al 2007[22]	1	58, F	Fib	I		NR		12	Multiple in the lung
Gladin et al 2007[23]	2	58, M	Fib	I		Petrous dural sinus	1	13	Multiple in the lung
		47, M	Trans	I		Right frontal		11	Multiple in the lung
Fulkerson et al 2008[24]	1	54, M	Fib	I		Intraventricular	1	Concurrent	Multiple in the lung
Ishibashi et al 2008[25]	1	68, M	N	I		NR		26	Multiple
Estanislau et al 2009[26]	1	75, M	Atypical	II		Right temporoparietal		6	Multiple
Psaras et al 2009[27]	1	65, F	Men	I		Parietal		15	Multiple in the lung
Lee et al 2009[28]	1	68, M	Trans/atypical	I, LATER II	II	Right intraventricular		0.5	Multiple
Etienne et al 2010[29]	1	58, M	Atypical	II		Right hemisphere		6	Multiple in the lung
Brennan et al 2010[30]	1	74, F	Atypical	II		Parasagittal	1	22	Multiple in the lung
Kanzaki et al 2011[31]	1	52, F	Atypical	II		Supratentorial		16	Multiple in the lung +brain
Alexandru et al 2011[32]	6	67, M	Anaplastic	III		Bifrontal		NR	NR
		26, F	Anaplastic	III		Multiple supratentorial		NR	NR
		84, F	NR	I		Right frontal		NR	NR
		38, M	Atypical	II		Right left sphenoid		NR	NR
		52, M	Atypical	II		Multiple supratentorial		NR	NR
		57, F	Anaplastic	III		Multiple supratentorial		NR	NR
Sabet et al 2011[33]	1	62, F	Anaplastic	III		Left frontal		Concurrent	Multiple in the lung
Lambertz et al 2011[34]	1	65, F	Anaplastic	III		Right frontal		1	Multiple in the lung + liver, skin
Taieb et al 2011[35]	1	30, F	Men	I		Left frontal		15	Multiple in the lung + liver
Nakayama et al 2013[36]	1	25, F	Men	I		Right parietal		0.5 earlier	Lung + diaphragm
Lanfranchi et al 2013[37]	1	74, M	Atypical	II		Right frontal		4	Lung + liver
Ocque et al 2014[38]	2	47, M	Atypical	II		NR		NR	Multiple in the lung
		44, F	Anaplastic	III		NR		NR	Multiple in the lung
Frydrychowicz et al 2014[39]	2	72, F	Atypical	II		Left parieto-occipital		11	Lung
		45, F	Atypical	II		Left frontal		5	Multiple in the lung
Reported cases	2	61, F	Anaplastic	I, LATER III	III	Frontal parasagittal	1	12	Lung + spine, adrenal gland
		62, F	Anaplastic	II, LATER III	III	Torcular	1	14	Multiple in the lung + liver, kidney
Nakaya et al 2018[40]	1	91, F	Atypical	II		NR		1	Lung
Kok et al 2018[41]	1	49, F	Meningothelial	I	I	Sphenoid			Brain
Baeesa et al 2018[42]	1	29, M	NR	I	III				Spine
Bhanusali et al 2018[43]	1	68, F	NR	I	I	Right parietal	1	11	Brain
Du et al 2018[44]	1	54, M	NR	I	I	Right frontal sagittal sinus	1	1	Lung
Mukherjee et al 2018[45]	1	81, M	Meningothelial	I	I	NR			Bone
Corniola et al 2017[46]	1	74, M	Anaplastic	III		Spheno-orbital	1	2	Lung
Honda et al 2017[47]	1	3, M	Anaplastic	III	III	Falx cerebri		1	Liver
Cho and Yoon 2017[48]	1	43, M	Men	I		Parietal		1	Multiple in the lung
Paix et al 2017[49]	1	43, F	NR	II		Parietal	1		Bone
Mindermann et al 2016[50]	1	54, M	Men	I		Tentorial			Liver, bone
Thomas and Dalal 2016[51]	1	58, F	Anaplastic	III		NR		15	Multiple in the lung
Kessler et al 2016[52]	6	24, F	Falcine	I	I	NR		11	Multiple in the lung
		69, F	Falcine	I		Left frontal			NR
		54, F	NR	II	III	Left parietal	1		Brain

NR, not rated; WHO, World Health Organization.

Continues

Table 1. Continued

Author	N	Years, Sex	Histology	First Surgery WHO Grade	Progression	Location	Sinus Involvement	Years to Recurrence	Organs
		66, F	NR	III	III	Right forehead		1	Lung + brain
		49, M	Atypical	II		Fronoparietal	1		Brain
Chua et al 2016[53]		26, F	Atypical	II		Parasagittal	1	1	Multiple in the lung + liver
Leemans et al 2016[54]	2	62, M	Men	I		Parasagittal		15	Multiple in the lung
		68, M	NR	III		Superior sagittal sinus	1	2	Multiple in the lung + liver
Nishida et al 2016[55]	1	68, M							NR
Kakkar et al 2016[56]	1	37, M	Rhamboid	III		NR	1	1	Multiple in the lung + bone, lymph nod
Wang et al 2015[57]	1	57, F	transitional	I		Middle fossa		1	Multiple in the lung
Forrest 2014[58]	3	80, F	NR	I		Right parietal			Liver
		68, M	Men	I	I	Cavernous sinus	1	1	Multiple in the lung
		68, M	Men	I		Right sphenoid bone			Liver
Attuati 2018[59]	2	48, F	Men	I	III	Parasagittal	1	2, 9	Lung + spine, adrenal gland
		47, F	Atypical	II		Torcular	1	7	Multiple in the lung, liver kidney

NR, not rated; WHO, World Health Organization.

Table 1. Summary of the Patients Reviewed from the Literature

Table 2. Summary of Epidemiological and Clinical Data of Case Report or Clinical Series Described in the Literature

Patients epidemiology	Total: 168 M: 80 F: 85 Average age: 55.7 years (range, 8–100 years, SD ± 17.2 years)	In 3 patient sex data were not reported
WHO grading	I: 40.5% II: 31.5% III: 22.1%	In 5.9% the grade was not reported
Involving dural venous sinuous	37	22%
GTR	116	69%
Subtotal/partial surgical resection (Simpson 4)	52	31%
Mean number of resection or re-treatment	2.65	
Adjuvant radiotherapy	46	27.4%
Radiosurgery	7	4%
Chemotherapy	18	10%
Mean time of metastatic spreading (years)	5.6	
Mean time of follow-up after metastatic spreading (years)	5	
Mortality	33	19.6%

GTR, gross total resection; SD, standard deviation; WHO, World Health Organization.

Table 2: Summary of Epidemiological and Clinical Data of Case Report or Clinical Series Described in the Literature

Table 3. Localization of Metastatic Spreading in Meningioma Reported in the Literature

Site of Metastases	Number of Metastases and Frequency (%)	Single Organ Metastases and Frequency (%)	Two or More Organs and Frequency (%)
Lung	106 (48.2%)	79 (35.9%)	25 (11.3%)
Spine	41 (18.7%)	21 (9.5%)	21 (9.5%)
Skeletal bone	25 (11.4%)	7 (3.2%)	19 (8.7%)
Liver	21 (9.5%)	7 (3.2%)	15 (6.8%)
Subcutaneous tissue of posterior neck, lymph nodes, parotid glands	14 (6.3%)	10 (4.6%)	4 (1.8%)
Other rarer sites	13 (5.9%)	2 (0.9%)	10 (4.6%)
Total	220 (100%)	126 (57.3%)	94 (42.7%)

Table 3. Localization of Metastatic Spreading in Meningioma Reported in the Literature

CHAPTER 3

3.1 Background and General Introduction

During my PhD program I focused my attention on the encouraging clinical and radiological results of benign skull base tumors and specifically of vestibular schwannomas (VS) treated with GK-SRS.

VS are benign, encapsulated, slow-growing tumors that origin from the vestibulo-cochlear nerve (VIII cranial nerve).

They can have intracanalicular or extracanalicular localization with extension at the ponto-cerebellar angle (CPA), inside the cochlear and the labyrinth. Larger tumors can displace and compress cerebellum and brainstem.

Upholding or improving quality of life is the central concern in counseling and treating a patient with VS. Standard management of VS includes observation with serial magnetic resonance imaging (MRI) and audiograms, microsurgical resection, radiotherapy, and radiosurgery. In neurofibromatosis type 2 (NF2) patients, chemotherapy with bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor, has also been reported [1].

Preservation of neuronal function is essential, and the management options of waiting, microsurgery and stereotactic radiation should be custom-tailored to the individual situation of the patient.

Microsurgery has been the primary active treatment of VS for many years, together with primary observation [2]. However, comparative studies have shown an increase of 30–45% in the risk of deterioration of quality of life after VS surgery [3].

GK-SRS is currently the most common treatment for small and medium-size VS but has also demonstrated satisfactory results with larger lesions [3-10]. In addition, the combination of surgery with radiosurgery for incompletely resected tumors is a proven compromise of tumor control while mitigating both radiation and surgical risk.

Hearing preservation, facial nerve function and tumor control remain the primary benchmarks used to evaluate treatment effectiveness and compare outcomes.

Hearing preservation rates after observation, radiosurgery, and microsurgery for small to medium size VS in large series is respectively 58.9, 60.2 and 4.3%, whereas corresponding rates of tumor controls is respectively 71.1, 97 and 94.3% [10].

Useful hearing preservation rate after radiosurgery is 47–77% at 3 years, 28–64% after 5 years and 23–45% at 10 years [7-9]. The median follow-up period in the largest series range from 3 to 10 years [7-9]. Although the favorable results in terms of tumor control, morbidity

and mortality rate if compared to surgical excision, hearing deterioration represents the main unsolved drawback of GK-SRS procedure especially for younger patients. With multiple noninvasive management options available, the tolerance of cranial neuropathy in patients with small to medium-sized tumors is low [1,5-6]. Many factors influencing hearing outcome (patients age, hearing status before irradiation, tumor stage, tumor intrameatal part extension up to fundus, tumor shape, nerve of tumor origin, presence of cystic changes in the neoplasm, cochlear dose, marginal dose or treatment modality (single section or fractionated) were investigated, but only few data are statistically significant and the influence of these variables on long-term hearing preservation are not well known [9, 10-15]. The interest in preserving the integrity of the cochlear nerve is increasing, also in the perspective of a future hearing rehabilitation involving thus a multidisciplinary team.

The union between neurosurgeons, otologists and radiotherapist has always aroused great interest in me and for this reason the following clinical study was carried out involving a multidisciplinary team.

After a brief introduction explaining general information on VS and GK-SRS, the field of inquiry investigated in this study was focused on the analysis of hearing outcome in VS after a long term (more than 10 years) follow up from GK-SRS. The study entitles "Long Term Hearing Outcome After Vestibular Schwannoma Steretotactic Radiosurgery with Gamma Knife" and was designed to identify factors influencing audiological outcomes in a long-term follow-up and the impact of hearing loss on quality of life. Data were collected retrospectively and prospectively in the period 2018-2021

The Prospective Observational Study, approved by ethics committee (protocol number: NCH01-20) of San Raffaele University Hospital, Milan, Italy on April 8, 2020, was developed at the Department of Neuroscience and Psychiatry, Sapienza University of Rome, Department of Sense Organs, Sapienza University of Rome, Department of Ear, Nose and Throat, San Raffaele University Hospital, Milan, Italy and at the Gamma Knife Section of Department of Neurosurgery and Radiosurgery Units San Raffaele University Health Institute.

3.2 Vestibular schwannoma

Vestibular schwannomas are commonly described in the United Kingdom as 'acoustic neuromas. The term 'Vestibular Schwannoma' (VS), reflecting the cell and nerve of origin of the tumor. The two nomenclatures are both accepted; however, vestibular schwannoma (VS) is recommended by the National Institute of Health Consensus document (Eldridge and Parry, 1992).

Sporadic VS is basically distinct from Neurofibromatosis type 2 (NF2). If it is not specificized in the text, VS refers to the sporadic tumor.

Cystic vestibular schwannoma (CVS) should be distinguished from solid vestibular schwannoma (SVS) because of their variant clinical, radiological, histopathological features and worst outcomes.

3.2.1 Anatomical considerations

VS are benign tumors arising from the perineural Schwann cells of the vestibular component of the VIIIth cranial nerve (the vestibulo-cochlear nerve).

The VIIIth cranial nerve arise in close relationship with VIIth (facial nerve) from the brainstem at the junction between medulla and pons, near the lateral end of the pontomedullary sulcus. As the nerve leaves the pons, crosses the cistern of the cerebellopontine angle (CPA) in its middle complex. The CPA middle neurovascular complex includes the anteroinferior cerebellar artery (AICA), pons, cerebellopontine fissure, the petrosal surface of the cerebellum, and the VIth (abducent nerve), VIIth (facial nerve) and VIIIth cranial nerves. The VIIIth cranial nerve leaves the CPA to enter in the internal auditory meatus in close relationship with the VIIth cranial nerve. The position of the nerve is mostly constant in the internal auditory canal (IAC). The facial and superior vestibular nerves run above to the falciform crest cochlear, and cochlear nerve and inferior vestibular nerves runs below the transverse (falciform) crest. A second vertical crest (Bill's barr) divided the lateral meatus in four portions, where facial nerve runs into the anterosuperior parts, cochlear nerve into the anteroinferior part. The posterosuperior and posteroinferior parts contain the inferior and superior vestibular nerves respectively.

As the VIIIth nerve leaves the brainstem, it is initially covered by neuroglial cells (astrocytes and oligodendrocytes). Thus, 7 to 13 mm distal to the brainstem, Schwann cells sheath the nerve at the neuroglial-Schwann cell junction. VS tumors most commonly originate at the neuroglial-Schwann cell junction both in the IAC, or in the CPA medial to the medial limit

of the IAC (internal auditory meatus). This tendency to begin growth within the IAC and emerge into the cerebellopontine angle cistern gives rise to the typical appearance of a moderately large VS.

As tumor expand, may involve (displacing or distortion) cranial nerves (from Vth to Xth), cerebellar arteries, and parts of the brainstem and cerebellum.

In the meatus, tumors commonly expand by enlarging the meatus or eroding (less frequently) the vestibule and cochlea.

For unknown reasons, the inferior vestibular nerve seems to be more commonly the site of tumor origin than the superior: in a series of 200 consecutive cases Khrais (2007) found that 91% of tumors for which a judgement could be made (76% of the total) arose from the inferior nerve. Therefore, as tumor grows displace the facial and cochlear nerve anteriorly and the facial nerve is stretched around the tumor capsule.

3.2.2 Tumor classification

Generally, tumors are classified according to their size and extension.

VS are classified according to their size in their largest extrameatal diameter (extrameatal extension) and compression of the brainstem, following guidelines produced at the Consensus Meeting on Reporting Systems on Vestibular Schwannoma (Kanzaki, 2003) [16]. The VS tumor size should be measured on MRI images, and the maximum diameter (also called tumor diameter) means the one measured in CPA along the long axis of tumor. The type of tumor within the IAC should be classified separately. Four commonly used tumor grading are Sterkers classification, House classification, Koos classification and Samii classification [17-20].

The Sterkers and House classification are mainly based on tumor size, while Samii and Koos are based on the anatomical relationship around the tumor. Koos classification combines the tumor size and anatomical relationship for larger tumors.

The Koos grading scale, a reliable method for tumor classification, is the commonest classification used for VS. (FIG 1)

This classification identifies four main tumor grades:

Grade 1: tumors involve only the internal auditory canal.

Grade 2: tumors extend into the cerebellopontine angle, but do not encroach on the brainstem.

Grade 3: tumor fills the entire cerebellopontine angle.

Grade 4: Vestibular Schwannoma displaces the brainstem and adjacent cranial nerves.

As an alternative the Sami-Koos stage, commonly used in scientific report identifies six main tumor grades:

T1: tumor confining to the IAC

T2: surpassing IAC

T3a: tumor occupying CPA

T3b: tumor occupying CPA and contacting the brainstem without compression

T4a: tumor compressing brainstem

T4b: severe brainstem compression displacement and deformation of the IVth ventricle under tumor compression.

Some authors have proposed a classification system for the cystic appearance, eg, Piccirillo et al, who describe a system differentiating between central and thick-walled cysts (Type A) and peripheral and thin-walled cysts (Type B).

Tumor size (CPA maximum diameter)	Sterkers	House	Koos	Samii	Tumor Description
0 (Intracanalicular)	Tube type	Intracanalicular	Grade Ⅰ	T1	Confining to IAC
≤10 mm	Small	Grade 1 (Small)	Grade Ⅱ	T2	Surpassing IAC
≤15 mm		Grade 2 (Medium)		T3a	Tumor occupying CPA
≤20 mm	Mild				
≤30 mm		Grade 3 (Moderately Large)	Grade Ⅲ	T3b	Tumor occupying CPA and contacting the brain stem without compression
≤40 mm	Large	Grade 4 (Large)	Grade Ⅳ	T4a	Tumor compressing the brain stem
>40 mm	Huge	Grade 5 (Giant)		T4b	Severe brain stem displacement and deformation of the fourth ventricle under tumor compression

Fig. 1 Main grading systems for acoustic neuromas.

3.2.3 Histopathology

Two different tissue types may be present in VS: Antoni type A tissue, which is compact and ordered with a palisading architecture, and Antoni type B tissue, which is myxoid and loose.

Antoni type A pattern is characterized by elongated cells are densely packed and arranged in fascicles. Palisades are sometimes seen; when prominent these form Verocay bodies. Antoni type B pattern cells are less compact and are prone to cystic degeneration. The importance of cyst formation within tumors is significant to tumor natural history Macroscopically, VS appear as benign encapsulated neoplasms of Schwann cells (WHO grade I). They arise eccentrically from their parent nerve, with the nerve fibers splayed along their surface (as distinct to neurofibromas which arise within the nerve).

Cystic VSs represent a subtype of VS. Cystic VSs tend to be large at diagnosis; they can demonstrate rapid and unpredictable growth, with a significantly shorter duration of symptoms. The rapid growth of cystic VS is attributed to expansion of the cystic component.

3.2.4 Molecular genetics

Although this study addresses only the management and natural history hearing loss of sporadic VS, it is important to recognize that 5% of vestibular schwannomas are associated with the congenital disorder neurofibromatosis type 2 (NF-2). NF-2 is a condition characterized by multiple vestibular, spinal and other schwannomas, meningiomas, ependymomas and ophthalmic lesions and in this syndrome the bilateral deafness may have devastating effects of Qof. NF2 is caused by a deletion in the tumor suppressor protein (TSN) ‘merlin’ or ‘schwannomin’, coded by the location 22q12 chromosome.

Merlin appears to have a role in human embryogenesis, in the regulation of growth factors, and in the interaction between the normal Schwann cell and the axon in peripheral producing cells morphologically characteristic of schwannomas (Nakai, 2006).
Another field of interest has been the exploration of the significance of angiogenic factors in the development of vestibular schwannomas. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) were found in larger, more vascular VS with greater volume during a shorter period of symptoms. The aim of the molecular studies briefly described above is both to understand pathogenesis and to identify potential medical treatment both in NF2 and sporadic VS.

3.2.5 Epidemiology

VS represent about 6–7% of all intracranial tumors, however, with 90% they are the most frequent lesion appearing in the PCA [16]. The annual incidence amounts to 1:100,000.
VS are more common in females than males with a ratio of 2:1. Some authors assume a hormonal process for the development of vestibular schwannomas [16].
The tumor may appear in every age of life, but the main manifestation
is between the 3rd and 5th decade. VSs in children are very rare and will usually form part of an NF2 syndrome.

3.2.6 Clinical features of disease: symptomatology

Traditionally, the symptoms produced by vestibular schwannomas are either otological or neurosurgical. Patients will often present with a combination of symptoms, and otological symptoms will almost always precede neurosurgical compromise, rarely found in smaller tumors.
Otological symptoms are characteristically unilateral. The most common symptoms include an ipsilateral progressive hearing loss, which may be of varying severity up to complete deafness, tinnitus, and dizziness. On rare occasions (less than 1%), hearing loss may be sudden in onset. VS has a natural history of hearing loss, which is caused by a combination of auditory nerve compression and cochlear dysfunction due to ischemia, infarction, or invasion.
When functional hearing deteriorations occurs, the benefits of binaural hearing are lost.
The audiological impact of sporadic VS in patients with normal contralateral hearing is mainly the loss of binaural hearing. This comprises a diminished summation effect (identical signal arriving at both ears), a reduction of the squelch effect (ability of the brain to separate noise and speech coming from different locations), and the head shadow effect (speech discrimination when the head is between the source of the sound and the hearing

ear). Patients with SSD, have problems in understanding speech in a noisy environment and cannot localize direction of sounds. Tinnitus is the second most reported symptom and will usually occur in combination with hearing loss. Although the tumor arises from the vestibular component of the VIIIth nerve, patients rarely complain of balance disturbances as their primary symptom probably because of the slow rate of tumor growth allows the vestibular system compensation. Small intracanalicular tumor (Samii-Koos T1) may cause mild symptoms of imbalance or occasional brief attack of vertigo whereas large tumors (Samii-Koos >T3) can develop ataxia due to tumor compression of the flocculus of the cerebellum.

The natural history of tumor grows, and possible effect of the different treatment options may prove debilitating, involving the fifth (trigeminal), seventh (facial), pairs of cranial nerves, brainstem, and cerebellum.

The VIIth (facial) appears to particularly resistant to damage. Trigeminal symptoms are more common, and usually a sign of a larger tumor with a component involving the under-surface of the trigeminal nerve as it emerges from the pons. Generally, the sensory roots of the nerve are affected with motor branches intact.

Presentation of the vestibular schwannoma can sometimes be emergent, usually due to hydrocephalus development.

The hydrocephalus seen in vestibular schwannomas is of an obstructive type caused by compression of the 4th ventricle by large tumors.

3.3 Hearing ability

3.3.1 Anatomy

The function of hearing, the sense of sound perceiving, is contained within the lateral skull base and temporal bone. The auditory system consists of three major parts:

The external ear: formed by the pinna and the external auditory canal, which receives sounds and transmits them to the middle ear via the eardrum.

The middle ear: includes the ossicles (malleus, incus and stapes) and the Eustachian tube, The three ossicles form a bridge between the eardrum and the inner ear through the oval window that covers the cochlea. The Eustachian tube connects the ear to the outer part of the nose and acts as an equalizing valve.

The inner ear: includes the cochlea, a structure that has a spiral shape like a snail shell, and it is located in the bony labyrinth, which has several membranous sections filled with fluids called endolymph and when these liquids move, they create fluctuations in the cochlea's hair-like structures called stereocilia. Finally, the Organ of Corti transforms the mechanical energy of the sound waves into nerve energy by creating electric impulses that are sent to the brain through the auditory or vestibulocochlear nerve.

3.3.2 Measurement and Classification of Hearing ability

For patients with serviceable hearing, hearing preservation is a key treatment goal in VS management. Hearing assessment is fundamental to the diagnostic evaluation of patients preparing to undergo surgery or SRS.

Hearing is measured by trained clinicians, usually audiologists.

Routine audiometry measures hearing thresholds using pure (single-frequency) tones at predetermined frequencies. The most important frequencies are then averaged together to provide the pure tone average (PTA): the average volume threshold of sound detection. The 4-frequency PTA typically combines 0.5, 1, 2, and 3 kHz and was recommended by the 1979 American Medical Associate (AMA) guidelines for calculating hearing handicap [21].

The other evaluated function is the word recognition (or speech discrimination) score (WRS or SDS) a score of the number of words correctly repeated, expressed as a percentage of correct (discrimination score) or incorrect (discrimination loss). The WRS provides information regarding the clarity of hearing and more specifically, the ability to discern words. A decreased WRS is a functional hearing impairment that cannot be rectified by simply increasing volume with a hearing aid. Retrocochlear pathology will often affect WRS disproportionately when compared with changes in PTA. Retrocochlear-pattern hearing loss is classically associated with "rollover" phenomena: decay of the speech discrimination

score with increased stimulus intensity. In common with other sensorineural hearing losses and in contrast to conductive hearing loss, the functional hearing loss as measured by speech discrimination thresholds is often more severe than that suggested by pure tone audiometry. A common audiometric sign of VS is the progressive speech discrimination decline that is worse than expected for the degree of hearing loss. Patients affected by unilateral VS showed unilateral or asymmetric sensorineural (SN), down-sloping / high frequency hearing loss with decrease of speech discrimination. Single-sided deafness (SSD), the unilateral sensorineural deafness in the poorer ear, with normal hearing in the opposite ear, is one of the most often consequences of the growth and therapy of the VS.
The useful hearing Measurement and Classification Systems are

3.3.3 Gardner–Robertson Scale (1988)

The Gardner–Robertson hearing scale (GR) is the first widely adopted hearing classification [22].
This scale identified 5 class of hearing according to PTA, speech reception threshold (SRT), and Speech discrimination (%). According to these parameters it is possible to differentiate serviceable from non- serviceable hearing.
Serviceable hearing (or useful hearing) result in PTA of ≥ 50 dB with a SDS of 50% or better

Table 1 Gardner–Robertson classification for hearing preservation

Class	PTA or SRT (dB)[a]	Speech discrimination
1	0–30 and	70–100
2	31–50 and	50–69
3	51–90 and	5–49
4	91–max loss and	1–4
5	No response and	No response

Abbreviations: PTA, pure tone average; SRT, speech reception threshold.
[a]Use better score. If PTA/SRT score and speech discrimination scores do not qualify for same class, use class appropriate for poorer of two scores.
Source: Reference 5.

3.3.4 1995 American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS)

In the 1995 AAO-HNS committee of Hearing and Equilibrium establishment a specific score for hearing outcome after hearing preservation surgery for VS resection [23].

The 1995 AAO–HNS guidelines was the first universal standard hearing outcome classification, identified 4 class of hearing based on PTA, and Speech discrimination (%) [23].

AAO-HNS Guidelines is based on PTA4 (500, 1,000, 2,000, and 3,000 Hz) and patient's word recognition score (Class I = 100–70% WRS; Class II = 69–50% WRS; Class III = 49–1% WRS; Class IV = 0%) Classified patients into one of four hearing classifications, that is, A, B, C, or D. A major limitation of were that patients could be classified into the same group but have very different functional hearing.

Table 2 AAO–HNS 1995 hearing classification system

Class	Pure tone thresholds	Speech discrimination (%)
A	≤30 dB *and*	≥70
B	> 30 dB, ≤50 dB *and*	≥50
C	> 50 dB *and*	≥50
D	Any level	< 50

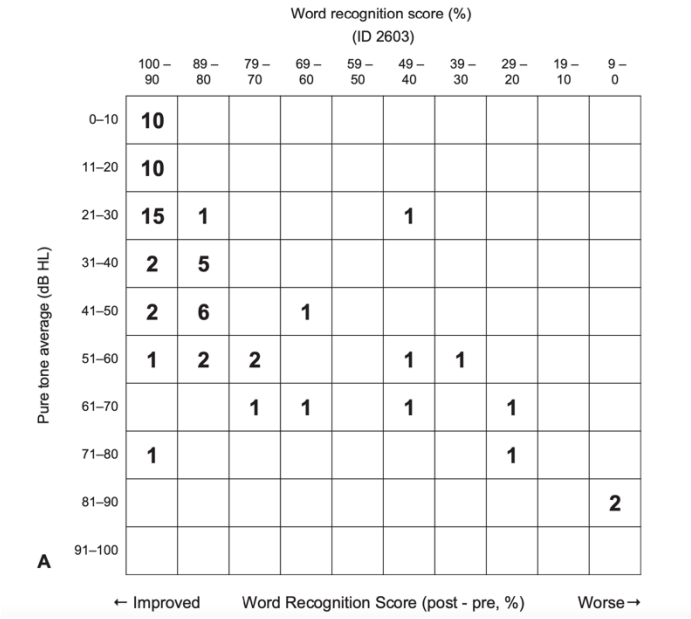
3.3.4 Guidelines/ 2012 AAO-HNS Guidelines

The 2012 AAO–HNS guidelines an update to the 1995 guidelines, made significant modifications to the 1995 guidelines to update the minimal requirements for reporting hearing outcomes after any intervention in addition to surgery, including stereotactic radiation, observation, or medical management, in which hearing outcomes are reported.

he 2012 AAO–HNS guidelines improved upon 1995 and GR guidelines by recommending the creation of a scattergram relating average air conduction PTA to the WRS [24].

Air conduction pure tone hearing thresholds are measured at 0.5, 1, 2, and 3 kHz. Since 3 kHz is not always recorded on routine audiometry, this can derive by averaging the 2 and 4 kHz values. Additionally, the WRS should be ideally measured using a validated recording in the patient's native language at a standard presentation level, such as a 40 dB or maximum comfortable loudness level. The postoperative or postintervention scattergram

only records the number of changes in response to the decided intervention and quantifies the extent of those changes.



Scattergram of pretreatment hearing results in a hypothetical sample of patients. Pure tone averages are represented on the Y-axis and word recognition scores are represented on the X-axis. Each number represents the number of patients whose audiometric data place them into a certain square

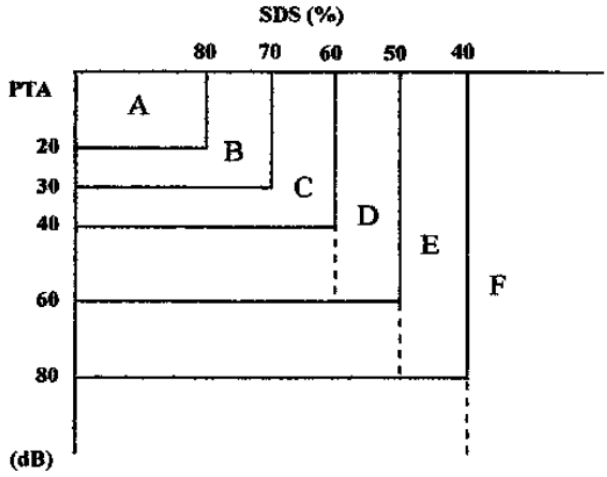
3.3.5 Tokyo scale

AAOHNS guidelines and the Consensus Meeting on Systems for Reporting Results developed the Tokyo classification [21, 23-24]. The Tokyo grading is as follows:

• Class A is defined as an average pure tone hearing equal
or better than 20 dB PTA and a speech discrimination score of at least 80%;

• Class B has the limit of 30 dB PTA/70% SDS;

• Classes C, D, E, F have a PTA of 20 dB steps and SDS of 10%, a better speech discrimination score than PTA makes the category of the outcome one class higher.



3.4 Facial nerve ability

The House-Brackmann Facial Nerve Grading System is widely used to characterize the degree of facial paralysis. In this scale, grade I is assigned to normal function, and grade VI represents complete paralysis. Intermediate grades vary according to function at rest and with effort [25].

Grade	Description	Characteristics
I	Normal function	Normal function in all areas
II	Mild dysfunction	Slight weakness noticeable on close examination May have slight synkinesis
III	Moderate dysfunction	Obvious difference on both sides, not disfiguring Noticeable (not severe) synkinesis Motion: • Moderate/slight movement of forehead • Complete eye closure with effort • Slight weakness of mouth with max. effort
IV	Moderately severe dysfunction	Obvious weakness and/or disfiguring asymmetry Rest with normal symmetry and tone Motion: • Without forehead movement • Incomplete eye closure • Asymmetry of the mouth with max. effort
V	Severe facial dysfunction	Slightly perceptible motion. Asymmetry Rest with asymmetry Motion: • Without forehead movement • Incomplete eye closure • Slight mouth movement
VI	Total facial dysfunction	No movement

3.5 Vestibular functions

3.5.1 Classification of the vestibular functions

Vestibular function tests together with audiological test are important for initial diagnosis of VS as well as subsequent monitoring of disease progression after treatment.
vestibular function is influenced by intracanalicular tumor length and diameter, therefore an impairment of vestibular function can be often observed even in small VS.
Vertigo are one of VS symptoms and one of the most important risk factors for the growth of VS.

The caloric test using videonystagmography (VNG) or electronystagmography (ENG) is used to measure la caloric respons in terms of slow-phase nystagmus velocities generated during warm and cold irrigations of each ear. When unilateral weakness (UW) is less than 25%, the caloric response is regarded as normal. it is possible to unilaterally stimulate the horizontal semicircular canal, which is innervated by the superior part of the vestibular nerve. Thus, one might think that the caloric response is only significant when the superior branch of the vestibular nerve is affected by the VS.

The Head Impulse Test use both the caloric irrigation and the head impulse test (HIT) to evaluate the horizontal vestibuloocular reflex (VOR). This test allows the identification of the covert saccades occurring during the head movement which are not visible to the naked eye.

Vestibular evoked myogenic potentials (cVEMPs and oVEMPs) provide information on otolith organ function. The conventional method for recording VEMPs involves measuring electromyographic activity from surface electrodes placed over the tonically activated sternocleidomastoid muscles. The cervical VEMP (cVEMP) is a manifestation of the vestibulocollic reflex. VEMPs can also be recorded from the extraocular muscles using surface electrodes placed near the eyes. These ocular VEMPs (oVEMPs) are a manifestation of the vestibuloocular reflex. VEMPs have an important clinical value in the diagnosis of VS because sometimes an abnormal VEMP result may be the only sign of a unilateral VS (the caloric and hearing test being normal)

Tinnitus is the perception of sound in the absence of an external sound. It is a frequent symptom of vestibular schwannoma (VS), occurring in more than half of all patients. Because tinnitus can reduce the quality of life in these patients, further evaluation of tinnitus in patients with VS should be routinely considered

Tinnitus Handicap Inventory (THI) is a 24 items questionnaire developed to value the severity of tinnitus handicap as well as predicting the psychological distress associated with tinnitus. Patients without tinnitus have a handicap score of 0 on the THI, and higher THI scores correspond to worse tinnitus

3.6 Tumor diagnosis

Magnetic resonance imaging (MRI), audiometry, and vestibular diagnostics are the mainstays of the clinical workup for patients harboring tumors.
High-field (1.5–3 Tesla field strength) magnetic resonance imaging (MRI) is the method of choice for detection, staging, and follow-up of vestibular schwannomas.
It is suitable for exact tumor volumetry in the follow-up as well as for preoperative assessment, of the tumor in relation to the brainstem, the fundus, the vessels, and nerves.
MRI is mandatory to plan SRS treatment. The scan protocol consists of T1-weighted (T1-w) and T2-weighted sequences without contrast enhancement, FLAIR (fluid attenuated inversion recovery), spin echo (SE) or turbo spin echo (TSE) before and after application of contrast media and thin-slice (=1 mm) T2-weighted 3D gradient echo (e.g. CISS = constructive interference in a steady state; FIESTA-C = fast imaging employing steady state), or 3D-TSE sequences. A diffusion-weighted images (DWI) sequence can be performed optionally to exclude/confirm acute ischemia.

The high-resolution T1-w sequence before and after application of contrast agent facilitates the detection of very small tumors and the postoperative evaluation (intralabyrinthine VS < 3 mm in size), especially the differentiation between scars and residual tumor tissue or recurrences.
CISS is highly sensitive and specific in the detection of small VS, approaching that of gadolinium-enhanced T1.

3.7 Stereotactic Radiosurgery

Among delivery techniques for VS radiosurgery, there are two main options: GK, the oldest and most studied technology that utilizes radioactive Cobalt-60 gamma emitting source, or linear accelerator (LINAC, including Ciber Knife) that uses multi-leaf collimators to shape the x-rays beam.
GK-SRS can be used exclusively for brain pathologies and has a higher accuracy (< to 0.15 mm). GK-SRS provides a rigid fixation using a head-frame based positioning ensuring an

intense dose of the target and the lowest dose to normal brain tissue. On the contrary, LINAC SRS, that is not designed exclusively for brain pathology, does not provide a rigid stabilization of the head during the procedure and a higher dose to the normal brain tissue is delivered compared with GK. According to literature, most of the available evidence of efficacy and safety in VS treatment with SRS are with GK-SRS.

Gamma Knife® surgery, is a non-invasive method for treating brain diseases. It is the delivery of a single, high irradiation dose to small and critically located intra-cranial volumes through the intact skull.

Lars Leksell (1907- 1986) a Swedish neurosurgeon was known as the father of stereotactic radiosurgery. In 1949 he developed the first stereotactic frame for clinical use which was fixed to the skull by 4 screws allowing any point within the skull to be defined by three Cartesian coordinates (x,y,z) of a point in three-dimensions. This frame restricts patient motion during imaging and treatment and allows placement of fiducial markers to localize the volume to be treated. In 1951 he constructed the first GK lesioning the target with stereotactical radiation. The first use of GK was aimed to treat functional disorders like movement disorders and tremor. The introduction of modern imaging techniques allowed GK to target tumors and AVMs. For patients with more complex or recurrent tumors and for patients with vascular malformations that have not been eliminated by open surgery or endovascular embolization, radiosurgery began an adjunctive and often decisive treatment option. Selected malignant tumors, especially solitary metastases, have responded dramatically to radiosurgery, obviating the need for craniotomy and prolonged hospitalization in this group of patients.

A multidisciplinary team of neurosurgeons, radiotherapist, medical physicists, radiologists, nurses, computer specialists, and physician assistants are involved.

The procedure is performed in four main steps:

1: Coordinate system acquisition

2: Imaging acquisition (MRI, CT, Angiography)

3: Treatment planning

4: patient positioning and treatment

3.7.1 Coordinate system

An MRI-compatible Leksell stereotactic head frame is positioned to patient head under local anesthesia to obtain a mechanical guidance to locate the patient in the GK coordinate system. The headframe allows patient to be moved to the dose focal point with sub-millimeter precision. During treatment, the stereotactic frame is moved to different x, y and z-coordinates to ensure radiation of the whole target.

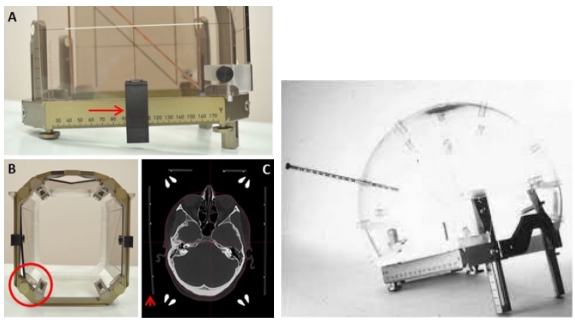


Fig 1-2

3.7.2 Imaging acquisition

The patient is then imaged using magnetic resonance (MR) or computed tomography (CT) imaging with a "localizer box" (Fig. 1-2) attached to the headframe.

High-resolution 1.5-T MRI scans are obtained with an appropriate fiducial system (Model Magnetom Vision, Siemens). Volume-acquisition studies required a 1-mm axial slice thickness, without a gap, T1- weighted with and without contrast-enhancement acquisitions that are reformatted in coronal and sagittal projections. The acquired images with patient fiducial markers are then used to plan the treatment.

3.7.3 Treatment planning

Among radiosurgical treatment, the Leksell Gamma knife1 Perfexion (LGKP), (Elekta Instruments, Stockholm, Sweden), is a completely redesigned system that was introduced in 2006. The treatment planning (dose calculation) for radiosurgery of vestibular schwannoma with LGKP equipment is done using a treatment planning system–TPS, called Leksell Gamma Plan1 (LGP), (Elekta Instruments, Stockholm, Sweden).

Images (i.e: DICOM data from MR imaging, T1, T2 and FIESTA) are uploaded into an Image software and then a multi-slice interpolation and automatic segmentation tools are used by the physicians to segment the organs at risk (OAR) and the target volume (TV). Each volume is then converted to a 3D structure volume and exported, in DICOM format, to Leksell Gamma Plan1 (LGP) software. In the LGP, the first step is to define the calculation matrix size. The Gamma Knife allow to focus a beam of 201 gamma rays on a single brain target.

The radioactive source used is cobalt.

The aim of dose planning is to cover at least 95% of the target with the lowest effective dose. Dose selection is based upon histology, target volume, prior radiation, latency from prior radiation therapy and location of the lesion.

To obtain a dose conforming, multiple isocenters are used, especially when the shape of target volume is irregular. Isocenter associated with an irradiation geometry are called

shots. Each frame position is termed a shot and, defined as irradiation of a given duration with focus at specified coordinates.

The collimator (shot) allows the radiation beams to intersect in a small focal point where the doses, delivered heterogeneously, are summated with lowest effect at the margin of the target. Outside the target there is a sharp dose fall. Each collimator can have sizes of 4, 8 or 16 millimetres or be blocked. The narrower the beams, the sharper the dose fall. Thus, the major limitation of GKS is the target volume, since big lesions require larger collimator sizes and therefore causes a less sharp dose fall.

Dose planning involves composing shots to develop a conformal isodose, including whole target and spares the surrounding tissue. The size of the collimator is selected based on the tumor shape and the gaps in coverage of the 50% isodose line displayed over the tumor. Shots are placed sequentially to cover the target as effectively as possible.

For each target volume defined, a calculation matrix is created, which automatically encloses the target volume.

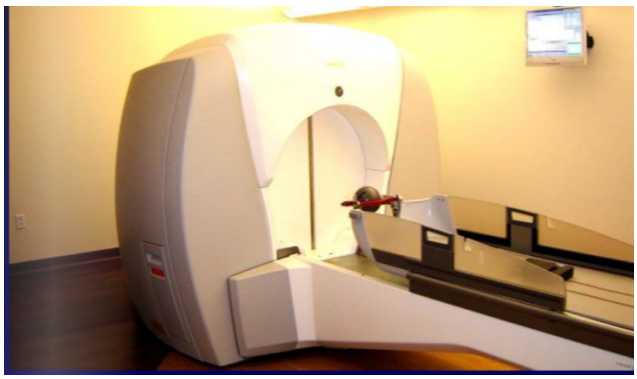
The isodose lines delineate radiation doses volumes of equal intensity and the radiation to the margin can be delivered to any % isodose line between 0-100. The 50 % isodose line is associated with the sharpest dose fall and the mechanical accuracy of the machine is in the submillimetre range.

The absorbed dose (Gy) is proportional to treatment time.

Treatment planning is performed using Leksell GammaPlan (Elekta). Final dosimetry and all treatment-planning variables are usually jointly approved by the neurosurgeon, the radiation therapist, and radiation physicist. The maximum dose varied from 20 to 32.6 Gy (median 26 Gy) and the margin dose from 11 to 15 Gy (median 13 Gy). The isodose line for the tumor margin varied from 40% to 63% (median 50%). The number of isocenters varied from 1 to 41 (median 12).

3.7.4 Patient positioning and treatment

An adapter is attached to the head frame, and this adapter fits simply into a head holder attached to the bed. Next, the patient's head is placed within a large helmet-like device with small openings called "collimator ports." Radiation beams are adjusted through these ports to direct the appropriate amount of energy precisely at the target tissue.



3.7.5 The aims of Gamma Knife Treatment for VS

The primary aim is local tumor control. Secondary aims include progression free survival, reduction in symptoms and improvement or maintenance of QoL.

1) **Local control** is defined as complete response with disappearance of the tumor, partial response with at least a 65 % decrease in volume, or stable disease (less than 65 % volume reduction and less than 40 % increase in volume.)

2) **Overall and progression free survival** is measured from the time of treatment until death or progression of the disease.

3) **Improvement in symptoms** can be subjectively reported by the patient (pain, seizure frequency) or objectively measured by clinicians (neurological deficits and neurocognition).

4) **QoL** is defined by the World Health Organization as an individual's perception of their situation and is a broad ranging concept, affected by multiple factors such as the person's physical health, psychological state, level of independence, social relationship etc.

3.7.6 Complications related to GK-SRS

1) **Local failure** is defined according to the response evaluation criteria in solid tumor, as at least a 20 % increase in the sum of the longest diameters, taking as reference the smallest diameter recorded since treatment started or a 40 % increase in volume (83).

2) Distant failure is occurrence of any new lesions distinct from the initially treated lesion.

3) **Acute adverse effects** from day 1 to day 90 after treatment

4) **Late adverse effects**

Grade 0: no signs of complications, grade 1: fully functional status with minor neurological findings and no medication needed, grade 2: neurological findings requiring steroids, anti-seizure medication or home care, grade 3: neurological findings requiring hospitalization

and grade 4: serious neurological impairment that includes paralysis, coma or seizures despite medication.

5) **Radionecrosis**: unintentional brain damage or tumor swelling caused by radiation. Radiation necrosis can cause temporary increase in volume or local changes in the contrast enhancement of the lesion with associated increase in surrounding oedema. It is caused by BBB damage, release of peptides from the radiated lesions or radiation damage of surrounding brain (endothelium, glial cells). It may be difficult to distinguish from local failure and repeated imaging to assess whether changes are transient, are necessary for final diagnosis.

6) **Neuropathy** due to radiation damage of healthy nerves is objectively measured by clinical evaluation or neurophysiological test or dedicated test.

3.7.7 The role of GK-SRS in VSs and hearing outcome

Since the first VS radiosurgical treatment in the 1979 [26], GKRS has been established as the most common first line treatment for small- to medium-sized VSs (Koos T3A; 25-30 mm in cisternal diameter) [4,9, 27-28]. Many studies have investigated and described as GKRS is an effective and safe treatment and many patients prefer radiosurgery to resection because of lower morbidity and lower hospitalization length than surgical resection [9].

Before radiosurgical treatment presentation of signs and symptoms should be accurately collect. Before and after treatment, hearing function can be evaluated according to GR modification of the Silverstein and Norell classification [22-23]

Tumor morphology, tumor volume, the length between VS intracanalicular portion and the fundus of the IAC, the distance between VS and the cochlea, are calculated and investigated from pre- and post-treatment MRI scans using GammaPlan software (Elekta).

The maximal inner dose should vary from 20 to 32.6 Gy (median 26 Gy), the marginal dose from 11 to 15 Gy (median ≤ 13 Gy). The maximum cochlear dose should not exceed 4 Gy to ensure hearing preservation [9]. The isodose line for the tumor margin varied from 40% to 60% (on average 50%). The number of isocenters can vary from 1 to 41 (on average 12) [9]. The application of a low-dose irradiation (marginal dose 11–13 Gy at 50% isodose line), results in 89–99% overall tumor control rates (93–95% at 5 years and 86–95% at 10 years after GKS) [**9**]. The use of lower margin doses (≤ 13 Gy) with a median mean cochlear dose of 4.0 Gy should reduce the risk of cochlear damage, but tumor control can be achieved with longer follow-up. Among the effects on hearing loss no significant difference between single and fractionated dose are reported in the literature [30].

Many investigators have reported relatively long-term hearing outcomes after SRS, but these results are still unsatisfactory, showing a serviceable hearing preservation rate of ≤ 50% over longer periods [9]. Many factors - patient's age, Gardner-Robertson (GR) hearing class before irradiation, Koos tumor stage, extension of the intrameatal part of the neoplasm up to fundus, tumor shape, nerve of tumor origin, presence of cystic changes in the neoplasm, cochlear dose, marginal dose, or treatment modality (single section or fractionated) - were widely investigated, but only few data are statistically significant [9].

A comprehensive analysis of Yang et al. and a systematic meta-analysis of Arthurs et al. [31-32] revealed a statistically significant correlation among serviceable hearing preservation and the use of marginal dose < 13 Gy. In their literature reviews hearing preservation was observed in 50- 60% of cases during 35-71 months of follow-up.

Yang et al. also reported that among 4234 included patients (followed-up on average 44.4 months, median 35 months) overall preservation of functional hearing was 51% (60.5% in patients receiving ≤ 13 Gy and 50.4% in patients receiving > 13 Gy) [31].

A retrospective series of Boari et al. described an overall hearing preservation rate of 49% during a mean follow up 59.9 months [9]. They showed in the multivariate regression model that pre-GKS PTA, difference between bilateral pre-GKS PTA, mean cochlear dose, fundus obliteration, use of a 4-mm collimator to the intracanalicular portion, and distance from the fundus and the tumor end were significant for hearing preservation, but the only statistically significant variable for GR class loss and functional hearing loss was the age >55 years. [9].

Frischer et al showed with a univariate regression analysis, that after 2 years follow-up of the GR hearing class prior to GKRS, Koos grade at GKRS, median cochlear dose, age at GKRS, prescription dose, radiation time, and target volume seemed to have a significant impact on the GR hearing class at the last follow-up. However, in the multivariate regression model, only the GR class prior to GKRS and the median dose to the cochlea were found to be independent predictors of the GR class at follow-up ($p < 0.001$ and $p = 0.029$, respectively) [27].

Tumor volume and its morphology are important parameters to predict the probability of hearing preservation after GKRS [27-28,33].

Tumors without whole IAC involvement, with a greater distance away from the cochlea, and less brainstem compression showed a better hearing preservation after GKRS [33-35].

For the contrary tumors with projection into intracanalicular portion (pear and linear type) are associated with a higher tumor length in the IAC and a worst hearing outcome [33].

Hearing preservation rates after radiosurgery have been correlated with total radiation dose delivered to the cochlea. Therefore, a median marginal dose ≤ 13 Gy and the maximum cochlear dose of 4 Gy are accepted values to ensure hearing preservation [35].

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3.8 Long term hearing outcome after vestibular schwannoma steretotactic radiosurgery with gamma knife

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Study design: Prospective observational study

Abstract

Sporadic vestibular schwannomas (VS) are unilateral benign slow-growing tumors arising from the eighth cranial nerve. The natural history or the effects of tumor treatment is characterized by different degrees of unilateral sensorineural hearing loss (SNHL). Gamma Knife Stereotactic Radiosurgery (GK-SRS) is now a well-recognized primary or adjunctive treatment option for small medium size VSs reducing perioperative morbidity and obtaining tumor growth control and preservation of cranial nerve function.

Patients who underwent GK-SRS for VS were retrospectively included in a database, and those with functional hearing before GK-SRS and aged less than < 70 were included in this prospective observational study. Each patient was re-evaluated at long term follow-up (>10 years) to assess residual hearing in quiet and in noise and quality of life measured by means of specific questionnaires such as: Hearing Handicap Inventory (HHI), Speech Spatial Qualities (SSQ), HAMILTON scale for depression and Tinnitus Handicap Inventory (THI).

The aim of the present study was to assess a >10 years long-term audiological outcome after VS GK-SRS, evaluating the perceptive and communicative point of view to assess the social impact of deafness on quality of life.

Introduction

The management of vestibular schwannomas (VS) includes observation with serial magnetic resonance imaging (MRI) and audiograms (wait and see strategy), microsurgical resection, and stereotactic radiosurgery (SRS) [1]. Treatment choice is influenced by symptoms, tumor size, grow pattern, cranial nerves and global neurological function, and patient preference [1]. All treatments carry on potential risks and benefits. Primary goals in the management of VS are to obtain tumor control, to prevent complications and to preserve cranial nerve function, including facial nerve function and hearing [2]. Despite a consistent number of small to medium size VS are treated conservatively [3], a wait-and-see strategy exposes patients to elevated risks of tumor growth and hearing deterioration [4]. The primary indications for resection of small-medium-size VS are brainstem compression, intractable trigeminal neuralgia or headache, hydrocephalus, an unclear diagnosis, and the patient choice [5-6]. Microsurgery, formerly recognized as the primary treatment for all tumor grades, has increasingly been replaced by stereotactic radiosurgery (SRS) [5-6].

SRS has been established as a first-line treatment option for small to medium size VS providing excellent tumor control and reduced morbidity [7-8].

Single-sided sensorineural down-sloping/high frequency hearing loss (SNHL) or deafness (single side deafness: SSD) are the most frequent consequences of the growth and therapy of the VS as well as speech discrimination impairment. In wait-and-see strategy spontaneous acute or progressive worsening of hearing are common.

When SSD occurs, the benefits of binaural hearing are lost. Patients with SSD have problems in understanding speech in a noisy environment and present difficult to localize the source of sounds. The exact pathophysiology of hearing loss in VS natural history is unknown. Possible causes are the compressive effect on cochlear nerve by VS, vascular occlusion of internal auditory artery or biochemical alterations of the inner ear fluids [9].

The mean hearing deterioration per year at 3, 5 and 10 years without any treatment (wait-and-see strategy), after microsurgery and after SRS range respectively from: 3 to 12 dB/year, 15 dB/year and 2-4 dB/year [10-12].

Although Gamma Knife SRS can be considered a minimally invasive out-patient procedure which has revolutionized the management of skull base surgery, it remains difficult to preserve long term hearing function. Factors associated with hearing preservation /degeneration has been investigated but remain discordant in literature [6, 13]. Possible investigated influencing factors on hearing outcomes after GKSRS are patients characteristics (age, audiological function before GK SRS), tumor characteristics (size, location, shape), radiosurgical planning (marginal dose, median mean cochlear dose) [6,10, 14].

Despite all, the progression of hearing loss remains the main unsolved problem of VS treatment for the possible negative impact of on patients quality of life (Qof) [14].

Hearing preservation ranges from 50 to 55% of the patients at 3-5 years from GK-SRS to decrease to 20-30% at 8-10 years [6,10,14]. Hearing deterioration within 3 years after GKS could be explained by ischemic or mechanical damage to the cochlear nerve due to high-marginal and cochlear dose, tumor coverage or nerve compression by transient expansion (tumor swelling) as swell [6, 10,15-16]. However, hearing acuity continues to deteriorate even beyond 10 years. Due to differences in length to follow-up, patient numbers, and methodology to collect and analyze side effects (analyses are limited to retrospective reviews), few results have been validated or reproduced and the causes of this progression are not well known.

The negative impact on quality of life of SSD in retrocochlear non-VS disease is well known [17-18]. Single side hearing deteriorations characterized by impairment in speech understanding in noise and sound localization, can be functionally devastating [17]. Binaural hearing remains critical to occupation performance for some professional figures especially in younger patients. Thus, characterizing hearing loss (HL) over time following treatment or conservative observation is critical, particularly in the setting of "benign" disease where patients are expected to live many decades after diagnosis and the treatment and effects of age-related HL will only compound hearing disability from disease [19]. The aim of the present study was to assess tumor control and hearing outcome at long term follow up (FU) (more than 10 years). Second objective of the study was to assess the social impact of deafness on quality of life in VS treated with GK-SRS after a long-term follow-up, in order to evaluate possible long term candidate predictors for clinical outcomes.

Hearing outcome was registered in quiet and in noise, and quality of life measured by means of specific questionnaires.

Materials and methods

Patients were retrospectively included in a database and prospectively re-evaluated by specific tests.

The following data has been retrospectively collected for each patient:

Patient Characteristics (age, sex, sporadic VS/VS-NF2) and pre-GK-SRS audiological assessment (audiometrical evaluation and GR class, PTA Ipsilateral and controlateral to GK-SRS) [20].

Pre-GK-SRS radiologic measurements (Volume, intracanlicular-fundus range) and tumor classification (according to the modification by Samii and Matthies of the Koos VS grading system) [21]

Radiosurgical technique and dose planning parameters (cochlear dose and marginal radiation dose)

Radiologic Tumor Measurements (volume variation: decreased, unchanged, increased) at first MRI follow-up (calculated from pre- and posttreatment MRI scans using GammaPlan software - Elekta)

Audiological assessment as GR class (GR I-V) at the first follow-up

Radiosurgical Technique

GK-SRS was performed with the Leksell Gamma Knife Model C (Elekta) until September 2007 and with the Gamma Knife Perfexion (Elekta) thereafter.

In both systems, patients were immobilized using a Leksell Model G frame-based system and T1, T1-weighted contrast-enhanced and T2-weighted magnetic resonance imaging (MRIs) imaged were acquired using a high-resolution 1.5T machine. Each patient was planned based on MRI and physical skull measurements. Treatment planning was performed using Leksell GammaPlan (Elekta). All patients were treated with a single fraction (13 Gy to the 50% to the isodose lines). Cochlea and modiolus dosimetry were monitored.

Post GK-SRS

In the prospective observational phase of the study, we included patients matching the following criteria:

GK-SRS for unilateral VS as primary and unique treatment

Follow up of 10 or more years

Patients age between 18 to 70 years old

Patients with functional hearing or limited HL (GR I-II) before GK

Audiological assessment with speech audiometry in quiet and in noise

Patients compliance.

The included patients have been prospectively studied at a long-term follow-up with:

A) Clinical evaluation (residual symptoms)

B) Audiological examination: a free-field pure-tone (Pure Tone Average: PTA) and speech audiometry (word recognition score WRS) both in unaided and aided conditions, a tonal audiometric examination (in free sound field, diffuse sound field, quasi-free sound field, with or without acoustic prosthesis) were performed in all cases. According to PTA serviceable hearing was defined as a pure tone audiogram result better than 50 dB on ipsilateral GK ear. The effects of loss of audibility on speech intelligibility were assessed with the speech reception threshold SRT in quiet. The effects of suprathreshold distortion were assessed in three conditions (noise from the front, NF, 0°; noise from the right, NR, 90°; and noise from the left, NL, 270°) by measuring SRTs in noise to investigate the amount of binaural squelch effect (BSE). The level of the noise was fixed at 50 dB, and the level of the speech was adapted to find the threshold. The Matrix analysis was developed to test a random selection of items. Each test list was composed by 30 sentences. Each correctly repeated word was recorded and scored (word scoring).

Each included patient has been evaluated with psychological tests to assess the social impact of deafness on quality of life.

C) To assess hearing in a complex scenario, the Speech, Spatial and Qualities of Hearing Scale (SSQ) test was assessed [22]:

SSQ test was used to measure hearing speech in a variety of competing contexts. Each of the 49 items was rated on a 10-point scale exploring many aspects of speech as perception (14 items), spatial hearing (17 items), and more general qualities of hearing, such as listening effort (18 items). The SSQ data were collected using a paper form. Each participant was asked to give a response, ranging from 0 to 10, corresponding to “not at all” and “perfect”. The average score across all 49 questions and the mean and median score of Speech, Spatial and Qualities of Hearing Scale were register.

Other comparative tests were Hearing Handicap Inventory Screening Questionnaire for Adults (HHI) and Hamilton depression scale [23-24]. Data were collected using a paper form.

A 25-question hearing handicap questionnaire exploring emotional (13 items) and situational (12 items) hearing handicaps was administer to all included patients. All the 25 items were measured using an ordered response with three possible answers: (‘Yes’=4, ‘Sometimes’=2, ‘No’=0). According to the total score three possible handicap degrees were identified: No Handicap (score ranging from 0 to 16), Mild to Moderate Handicap (score ranging from 17 to 42) and Significant Handicap (≥43) [23].

The Hamilton depression scale contained 17 items (HDRS17) [24]
A score of 0–7 was defined as normal range
A score of 8 – 17 was defined as light depression
A score of 18 – 24 was defined as moderate depression while a score of 25 or higher was indicative for severe depression.
The average score of Hearing Handicap Inventory Screening Questionnaire and Hamilton depression scale were register.
To assess the impact of dizziness on QoF each participate completed the Tinnitus Handicap Inventory (THI) questionnaire using an ordered response with three possible answers: ('Yes'=4, 'Sometimes'=2, 'No'=0). The final THI score of 0-16 means "no or slight handicap", 18 to 36 indicates "mild", 38 to 56 indicates "moderate", 58 to 76 indicates "severe", and a score of 78-100 is classified as "catastrophic handicap" [25].

The prospective observational phase of the study was performed at Cochlear Implant Centre, University Sapienza – Policlinico Umberto I – Rome and at the Department of Ear, Nose and Throat, San Raffaele University Hospital, Milan, Italy. Ethical approval was obtained by the Institutional Review Board of San Raffaele University Hospital (protocol number: NCH01-20). This observational study was carried out in accordance with the ethical requirements of the Helsinki Declarations, the Epidemiological Good Practice Guidelines of the ICH (International Conference of Harmonization), and the existing legislation in Italy.

Statistical analysis

Tonal audiometric results have been compared with the same data obtained before GK.
In predictive model loss of GR class and loss of functional hearing has been investigated also by screening the mean and maximal dose to cochlea, the mean dose to modiolus, the pre-GKRS GR class and PTA.
Univariate and multivariate models have been applied to investigate correlations between epidemiological, tumor and treatment variables and audiological and psychological outcome at last follow-up. Chi-squared, Friedman, Wilcoxon tests and Spearman rank correlation were non-parametric tests used to measure non-parametric statistics correlations. Spearman rank correlation was used to test the degree of association between two variables. The Pearson correlation coefficient was used to measures the strength of the linear relationship between normally distributed variables. Statistical analyses were performed using IBM SPSS Statistics for Windows (v 22.0, IBM Corp., Armonk, NY, USA). Data were expressed as median and interquartile range (IQR) or mean and standard deviation (SD) as specified in each case. Normal distribution of all variables was tested using

Shapiro-Wilk P values <0.05. Spearman rank-order correlations were used for bivariate correlations between variable that were considered statistically significant.

Results

Patient Characteristics

The analysis of our database started from 153 patients who underwent GKSRS as the primary treatment for VS with regular audiological follow-up. Out of these 153 patients, 57 (37.2%) were initially excluded because presented non-functional hearing at GKRS (GR class > II). Ninety-six patients had functional hearing at the time of GKRS and were analized to value the audiological outcome at the first follow-up (mean length of follow-up: 59.9 months) [10] (Fig 1). Therefore, we retrospectively reviewed a database of 96 patients treated for VS with GK-SRS at the Neurosurgery and Radiosurgery Units in San Raffaele University Health Institute from 2001 to 2010 who had useful hearing at the time of GKSRS [10]. Data of these 96 patients were previously included and published in a study aimed to assess the safety and efficacy of GKSRS, in terms of tumor control, hearing preservation, and complications [10]. Out of these 96, 74 (77.1%) were excluded due to exclusions criteria and 22 (22.9%) patients, meeting inclusion criteria, were included in the prospective phase of the study (Fig 1). 14 (63.6%) were males and 8 (36.3%) were females. Patient mean age at GKSRS was 42.5 y.o (median 43, SD 10.9) and the average age at last follow up was 56.4 y.o (median 57, SD 9.8). One patient was affected by Neurofibromatosis Type 2 (NF2). The mean duration of the first follow-up was 59.9 months, (maximum 153 months) and the duration of last follow up ranged between 120 and 228 months, with a mean of 167 months and a median of 156 months.

In 10 (45.5%) patients VS was on the right side and in 12 (54.5%) patients VS was on the left side. (Table 1).

Signs and Symptoms

Progressive hearing loss was reported in 16 (72.7%) patients at the time of GK-SRS, tinnitus in 12 (54.5%), vertigo in 3 (4.5%), CN VII impairment in 1 patient and CN V impairment/neuralgia was recorded in 2 (9%) patients.

Recurrent otitis was reported in 1 patient.

All included patients presented serviceable hearing at the time of GK-SRS: 12 (54.5%) patients were GR class I and 10 patients (45.5%) were GR class II. (Table 2)

Radiological and GK-SRS treatment data

The mean VS tumor volume at GK-SRS was 1.2 cm^3 (median 0.6 cm^3, range 0.09–1.7 cm^3, SD 1.5 cm^3). The distance between VS intracanalicular portion and fundus ranged between 9.7 and 0.1 mm (mean 4.4, median 0.6, SD 2.4 mm). Median pretreatment Samii-Koos was 2

(mean 1.9 SD 0.8). The mean marginal radiation dose was 13 Gy at isodose 50%. The average mean cochlear dose was 4.7 Gy (median 4.6, SD 1.6) and the average maximal cochlear dose was 9.2 (median 9.2, SD3). (Table 1).

Symptoms Follow-up

Symptoms as vertigo or imbalance were recorded in 3 patients (13.6%) at the last FU. Tinnitus remained stable in 9 patients out of 12 (75%) and worsened in 3 (25%). Facial and trigeminal impairment remained stable. (Table 2)

Tumor outcomes

At the first follow-up median value of tumor stage according to Samii-Koos classification remained stable to stage 2 (median 1.9 SD 1) after a transient tumor swelling (6-18 months) in 10 patients (45.5%). This value remained stable also at the last FU (mean 1.8, median 2, SD 1), despite in 8 cases (36.3%) tumor reduction was observed.

Tumor average volume at the last follow up was 1.0 cm^3 (median 0.7 cm^3 SD 1.1). At the last FU no patients required further treatment for VS and tumor control was achieved in all included patients (100%). (Table 1)

Hearing outcomes

At the first and last FU the mean value of GR was respectively GR class III and II.

At first FU serviceable hearing (defined as a pure tone audiogram result better than 50 dB on ipsilateral GK ear or GR class I and II) was recorded in 10 patients (45.4%): 3 patients (13.6%) was GR I and 7 (31.8%) patients GR II.

At the last FU serviceable hearing was recorded in 12 (54.6%) patients: 4 (18.2%) patients remain GR class I and 8 (36.4%) patients were GR class II. (Table 2)

Ten patient (45.4%) presented a non-serviceable hearing at last FU. Two of them already used hearing-assistive device at time of survey.

Hearing evaluation at the last FU was performed recording pure tone audiometry (PTA) by Tonal audiometric examination and the speech reception threshold (SRT) by Matrix test. For each patient the mean PTA was recorded in both ear (ipsilateral to GK and controlateral to GK). The mean PTA value before and at the last follow-up in the ispslateral and controlateral ear are summarized in table 3 and table 4.

The Speech reception thresholds (SRTs) for single syllables or words and sentences were analysed in quiet and in noise. All patients were tested in unilateral (ipsilateral and contralateral to GK ear) and bilateral listening conditions.

Signal-noise (S) (N) presentation was performed in three different conditions

S0/N0, S0/N-contra, S0/N-ipsi.

The mean SRT/quiet was 20.8 dB (median 25, SD 15), SRT noise Signal-front was -0.2 dB (median -0.5, SD 5.11); SRT noise Signal-ipsi -1.1 (median -1.7, SD 6.5) and SRT noise Signal-contra was -5.1 dB (median -6, SD 4.4).
The data on audiological outcome reported in the literature restricted to a population similar to that included into the present study are summariezed in Table 5.

Psychological data

Psychological evaluation at last follow-up was performed by SSQ, HHI, THI, Hamilton questionnaires.
The mean SSQ results was 80,7 (median 90 SD 32); the mean SSQ spatial results was 80,7 101.3 (median 110 SD 37.9); the mean SSQ quality 101.8 (median 117, SD 50.8).
The median score of HHI was 18 (median 10, SD 21.5) corresponding to mild to moderate handicap (score ranging from 17 to 42). The mean HHI-Emotional was 10 (median 8, SD 11) and the mean HHI-Spatial was 8.7 (median 6, SD 10.7).
The mean value of Hamilton depression scale was 8.2 (median 4, SD 7.5) (0-14/slight symptoms) corresponding to light depression.
The mean THI value was 12.8 (median 8, SD 12.9) corresponding to no or slight handicap.
The mean tinnitus intensity was 6.5 (median 5, SD 9.7) (0-43/moderate).

Discussion

The role and efficacy of SRS in VS treatment has been widely reported in the current literature [1-6]. Despite tumor control and low complication rate have been extensively investigated, hearing deteriorations remain an unresolved problem probably because the current analyses are limited to retrospective reviews or short term Follow up.

We had re-analyzed, 22 of 96 patients previously studied for hearing and tumor outcomes [10] (Figure 1). The results of the previously published study were qualitatively compared with the new results obtained prospectively after more than 10 years of Follow up from GK to better understand the behavior of predicting factors of hearing outcomes after more than 10 years of follow-up.

Tumors control al last >10 FU

In the previous published series of Boari et al (mean length of follow-up: 68.3 months) tumor control was achieved in 97.1% of the cases [10]. In 11 patients (2.9%), GK-SRS failed to control the tumor, 3 (0.8%) of these patients underwent a GK-SRS retreatment, and 8 (2.1%) underwent microsurgical resection. In 82.7% of the VSs a volume reduction was observed.

In our series of 22 patients, qualitative data show tumor swelling in the first 1–3 years after GK-SRS in 10 patients (45.5%). Since the incidence of tumor growth after GK-SRS (mainly in the first 13 months) ranges from 10% to 50%, this result corresponded to those reported in the literature [10].

Overall Samii-Koos stage remained stable after first FU ($p>0.05$), and no further treatments were needed, and no patient developed treatment failure after more than 10 years.

A significant Samii-Koos stage reduction was observed between pre-GK-SRS and more than 10 years of Follow up from GK-SRS ($p=0.007$). This variation remained significant between pre-GK-SRS and the Last Follow-up ($p= 0.002$). Tumor Samii-Koos stage reduction was registered between 1-year follow up from GK-SRS and the last follow up in 8 cases but this result was not significant ($p>0.05$).

According to literature tumor control rates with GK-SRS remains stable after 5 years [26].

In the main series 5- and 10-year tumor control rates range from 90 to 97.7% [27-28].

Among possible factors influencing tumor control or its failure, as patient age or gender, delivered treatment dose, tumor volume and tumor control, we observed that pre-GK Koos stage was positively correlated to tumor control ($r=0.7$; $p=0.003$) [27-31].

Our results were consistent with previous cohorts where late failures are extremely uncommon after 10 years [29,32-36]. This confirms that long term tumor control is possible, but given the limited samples, data of tumor control cannot be generalized.

Hearing preservation al last more than 10 years FU

Based on inclusion criteria, patients in the present series showed serviceable hearing at the time of GK-SRS: 12 (54.5%) patients were GR class I and 10 patients (45.5%) were GR class II. During follow-up a progression of hearing loss was observed: GR was respectively class III and II at the first and final follow up. Among 22 patients in 12 (54.5%) serviceable hearing was recorded: 4 (18.2%) patients remained GR class I and 8 (36.4%) patients remained or passed to GR class II. Ten patients (45.4%) presented a non-serviceable hearing at last FU. According to the literature serviceable hearing preservation rates after SRS progressively decrease from 55-90% at 1 year, 40-70% at 5 years, and 20-55% at 10 years [10, 24, 26, 27]. Our deteriorating rate was then expected.

Our results showed that pre-GK-SRS GR was significantly worsened both at the first 5 years FU ($p=0.01$) then after more than 10 years ($p=0.002$). (Fig 1)

Despite GR score overall got worsening, it was not significantly changed between 5 and 10 years follow-up ($p>0.05$), therefore the consistent GR hearing deterioration occurred within the first 5 years after GK-SRS.

This result was consistent with the previous series of Boari et al. where the hearing loss was higher in the first 2 years (highest in the first 12 months) after treatment (7.03 dB/year) than thereafter (2.39 dB/year) [10].

PTA evaluation at the last follow up become worse in the 77.3% of patients.

PTA deterioration was significantly worsened from pre-GK-SRS and both the first 5 years Follow up ($p=0.04$) and after more than 10 years of Follow up from GK-SRS ($p=<0.01$) ($r=0.5$-0.7;) meaning the strong correlation of hearing staging with PTA threshold.

The average PTA increased significantly both ipsiGK and contraGK ears, and the difference between ispiGK and contralateral ears was significant.

A hearing deterioration was observed in all frequencies in ipsiGK ear (250 = 1.0 (0-8) dB; 500 = 1.0(0.5-7) dB; 1000= 1.2 (0.5-8) dB; 2000= 1.7 (0.5-8.5) dB; 4000= 1.5 (0.5-9) dB, while contraGK ear hearing deterioration affected only high frequencies. (Fig 2)

An increased risk of high frequencies hearing deterioration in contralateral ear in patients with VS was reported and some authors observed that the progression of hearing loss in contralateral ear in VS patients was significantly greater than expected for unrelated age-associated hearing loss in the general population [37]. In a large series of Early et al. on 661 patients, the authors did not find significant correlation with patients by age, sex or tumor size and suggests that VS-secreted factors may affect hearing in the contralateral ear [37].

In our series at the last follow up non serviceable hearing in contralateral GK ear was registered in 1 patient; 3 patients were GR II and 2 of them required hearing aids.

Contralateral hearing progression in contralateral ear in our series should be probably ascribed to degenerative changes in the internal ear frequent in the advancing years (presbyacusis).

Nevertheless, this result can strengthen the finding that GK related hearing loss occurs mainly during the first 5 years.

The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) and the GR hearing classification scales are the two most applied measures used to quantify hearing outcomes in VS patients [17, 20]. Both define serviceable hearing as having at least a 50% speech discrimination score (SDS) and at most a 50-dB PTA, but if used to measure hearing loss and its life impact, can show serious limitations [38]. The categories included in these classifications are too generic to correlate with patient outcomes or satisfaction and the description "serviceable" hearing could be arbitrary. Audiological recognitions of PTA and WRS in quite do not reflect the real quality of understanding speech in noisy environments. Hearing impairment as consequence of VS is worst in adverse listening conditions (noisy environment) and patients categorized as GR I o GR II (serviceable hearing) could have serious limitations in social communication. The transition to class I to class II is far from equivalent to maintained serviceable hearing.

For this reason, in the prospective phases of the study we assessed patient communication ability also in noisy environments.

According to Matrix results the SRT with $Signal_0/Noise_0$ and $Signal_{ipsi}/Noise_0$ was significantly different ($p=0.01$): meaning an absent squelch effect, where signal from the VS side was too poor. According to this result in SSD of VS patients is related to the contralateral ear and the ability to listen in noise becomes worse when it is asymmetrical hearing between the 2 ears (Fig 3).

Predictors for hearing outcomes

According to literature patient, tumor and radiosurgical factors may influence hearing outcomes. Patient age at GK-SRS, GR hearing class prior to GKRS, Tumor dimension at GKRS and median cochlear dose are the most important and significant variables influencing hearing outcomes at the last follow up. However, the mean follow up ranges between 2 and 10 years in the large series [10, 6].

Patients' characteristics

Multiple studies have suggested that advanced age results in poorer hearing outcomes [10].

In the retrospective series of Boari et al. (the study from which this research is born) on 96 patients analyzed during a mean follow up of 59.9 months, the GR class loss and functional hearing loss were significantly correlated to young age (less than 55) [10].
In our series the probability of retaining functional hearing after more than 10 years was not influenced by age at GK.
Patients with better pretreatment hearing tend to have a higher probability for retaining serviceable hearing post-irradiation [10], but this result was not more significant in our series after more than 10 years.

Tumor characteristics

Analyzing the possible influence of tumor dimension (Samii Koos stage, pre-GK-SRS tumor volume, pre-GK-SRS distance between VS intracanalicular portion and fundus) on long term hearing outcome (GR class and PTA threshold), no significant correlation was recorded after 10 years.
Transient volume expansion (tumor swelling) has been correlated with hearing deterioration [39]. Some authors have argued that radiogenic tumor swelling may result in nerve conduction block as a result of compression forces [39-40]. Despite we observed transient tumor swelling at the first Follow up and a significant worsening of GR class between pre-GK-SRS and first GK-Follow up, the correlation among tumor dimension and GR worsening was not significant.
The correlation between GR class and tumor dimension at pre-GK-SRS, first follow up, and more than 10 years from GK-SRS was not significant in all follow up stages.
Moreover, also the hearing threshold did not show any correlation to Koos stage. Neither is Δ-worsening of GK ears (Fig 4).

Radiosurgical effects

A comprehensive analysis of Yang et al. and a systematic meta-analysis of Arthurs et al. in a period of 35-71 months of follow-up revealed a statistically significant correlation among serviceable hearing preservation and the use of marginal dose < 13 Gy [41-42].
Patients treated with radiation to the head and neck have been shown to develop late sensorineural hearing loss [43]
Although the exact mechanism is still unknown, possible cause of this damage could be the direct damage (compression) or the injury of the cochlear and auditory nerve fibers [44]. Microvessels can be obliterated from radiation leading to intimal thickening, vessel narrowing, or axonal damage [45].

Secreted factors, such as tumor necrosis factor alpha (TNFa), and extracellular vesicles (EVs) from human VSs NLRP3 inflammasome and the associated ototoxic molecules such as IL1b overexpression have been advocated to cause cochlear damage and HL progression as independent mechanism of mechanical compression of the cochlear nerve [46-50]

Among the investigated factors, mean Cochlear dosage is significantly correlated to PTA of ipsiGK ear (500-2000 Hz) in a very long follow-up, still controlling for Koos stage effect (rho= 0.71-0.878; p= 0.03-0.002) because Koos stage was not significantly changed between 5-10 years.

According to our results, hearing deterioration occurs especially within 3 years after GKSRS. Hearing function however continues to deteriorate after the first 1-3 years. Hearing function in the contralateral ear decreases but was almost unchanged 10 years after treatment, suggesting that hearing deterioration after the first 3 years in ipsiGK ear is not caused only by aging but also by radiation toxicity.

Psychological outcomes

Diagnosis and treatment strategy of VS can impact QoL. Compared to SRS, microsurgery presented worse psychological outcomes [8]. There is evidence that patients that underwent surgical resection for VS may experience a temporary decline in multiple, but mostly physical, QoL scores [8]. This temporary decline may depend on early surgical stress [8].

There is some evidence that patients with larger tumors (>3 cm) may experience a lower QoL when compared with those with smaller tumor, although this is not confirmed in all studies [51-52].

In the present series no significant correlation between tumor dimension after GK-SRS and psychological outcomes were found.

On the other hand, radiosurgery appears to have less effect on QoL as measured by the SF-36 but may impact some other aspect of patients' life such as facial weakness, dizziness, and hearing impairment [51].

Sensorineural hearing loss has cochlear in origin, but the entire auditory system works thanks to the integration of hearing, listening, comprehending, and communicating functions. The dynamic interaction between sensory and cognitive aspects of hearing can influence the audiological performance in real environments when binaural hearing is strongly implicated. In our analysis HHI score was strongly correlated to each domain of SSQ: speech (p=0.002); spatial (P<0.001); quality (P<0.001), SSQ total (P<0.002). These results suggest that in presence of hearing impairment (HHI) hearing disability is perceived across several domains. The ability of the listener to attend a specific conversation in presence of competing sounds or several similar speakers (quiet, constant noise, reverberation, many

other voices) is impaired such as the ability to define sound recognition, clarity/naturalness direction and distance, underlying the dynamic aspects of hearing capacity. Moreover, SRT N0/S0 and N0/Scontra were inversely correlated to SSQ (rho -0.49; p=0.05; rho= -0.6 to -0.64, p= 0.01-0.008), whereas SSQ Speech was inversely correlated to SRT front (rho -0.49; p=0.05) and significantly correlated to GK-PTA (rho 0.47; p=0.04). In our analysis HHI-Emotional Significantly correlated to ispi GK-PTA (rho 0.47; p=0.04), strengthening the hypothesis that the experience of handicap is mostly influenced by contexts but, presumably, the personal dimension of handicap also depends on an emotional component. Emotions may influence several aspects of cognitive processes, as perception, learning, memory, and problem solving. Emotion can impact on attention, especially modulating the selectivity of attention as well as motivating action and behavior.

SSQ total, Speech and Spatial are inversely correlated to speech perception in noise of the contralateral ear (rho= -0.6 to -0.64, p= 0.01-0.008) suggesting that single side deafness is quite tolerated in absence of audiological decline of the contralateral ear. Therefore, looking to the possibility of hearing rehabilitation, this depends on the impairment on the contralateral ear.

Among other symptoms tinnitus values have not significantly changed from pre-GKRS and THI score (median value 14 (0-43/moderate) was not correlated to PTA threshold, Gy total Depression symptoms

Hamilton questionnaire: Median value 4 «absent» (0-14/slight symptoms)

In our series only 2 patients at the last Follow up were ultimately utilizing long-term hearing-assistive devices, this suggesting, according to our psychological test results, that most patients sufficiently adjust to unilateral hearing loss or are unsatisfied with the benefits achieved with current device options.

Conclusions

After more than 10 years from SRS tumor control is still maintained and hearing outcomes remained stable. Hearing deterioration within 3 years after GKS can be due to several causes (tumor swelling, cochlear dose, marginal dose, age, GR class). However, hearing function continues to deteriorate beyond the first 1-3 years

Hearing deterioration beyond the first 3 years, although marginally influenced by ageing, is mainly influenced by radiation toxicity. After more than 10 years from SRS the personal perception of hearing disability is influenced by emotion and behavior component. The impact of single side deafness ion QoL can be tolerated in absence of audiological decline of the contralateral ear

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Figures

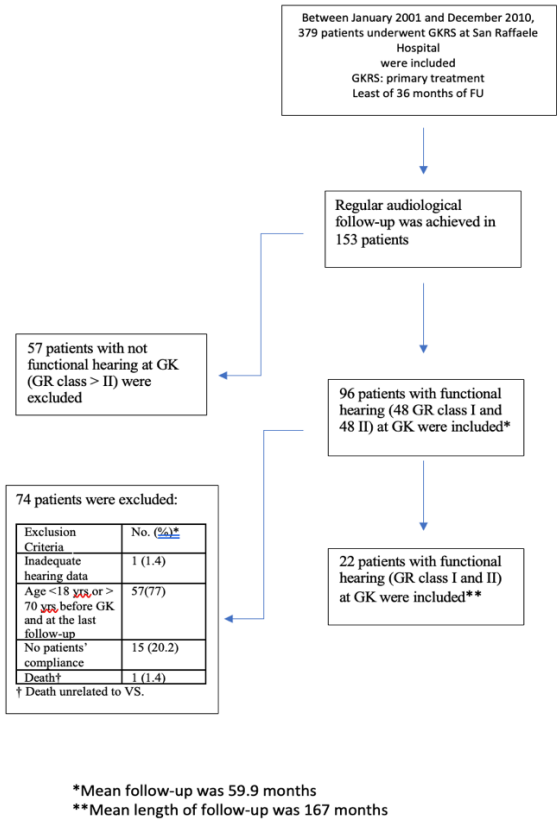


Fig 1: Flow-Chart graph: Summary of the process of patients selection

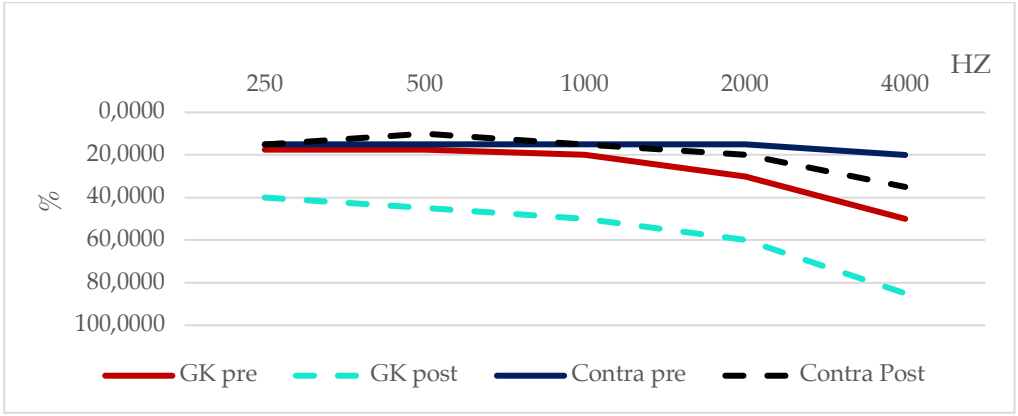
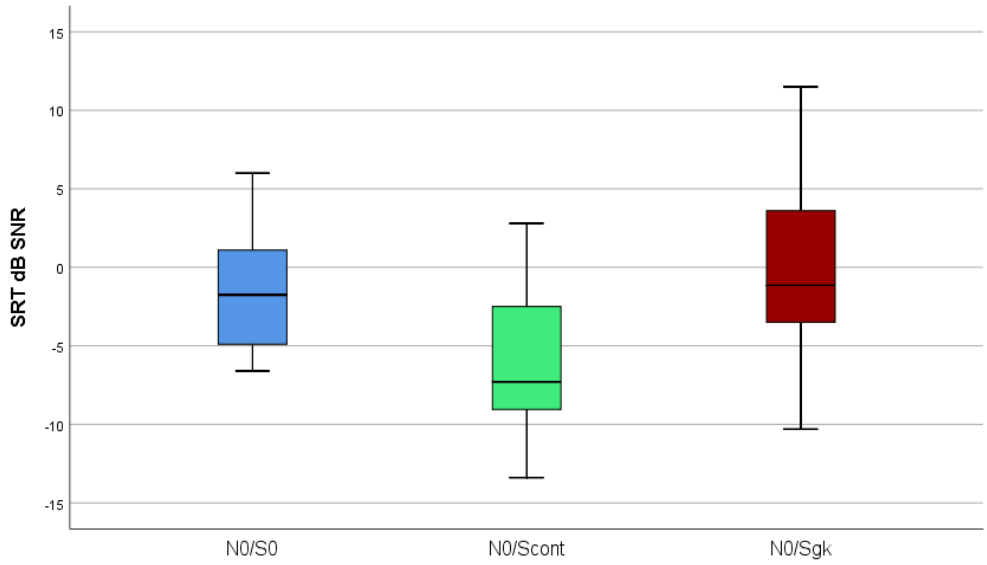


Figure 2: hearing loss at last follow-up GKpre: ipsilateral ear to gamma-knife before GK, GKpost: ipsilateral ear to gamma-knife after GK. Contra pre: controlateral ear to gamma-knife before GK, Contra post: controlateral ear to gamma-knife after GK



Fug 3: This graphic shows as SRT with Signal0/Noise0 and Signalipsi/Noise0 are significally different (p=0.01) meaning an absent squelch effect, where signal from the VS side is too poor

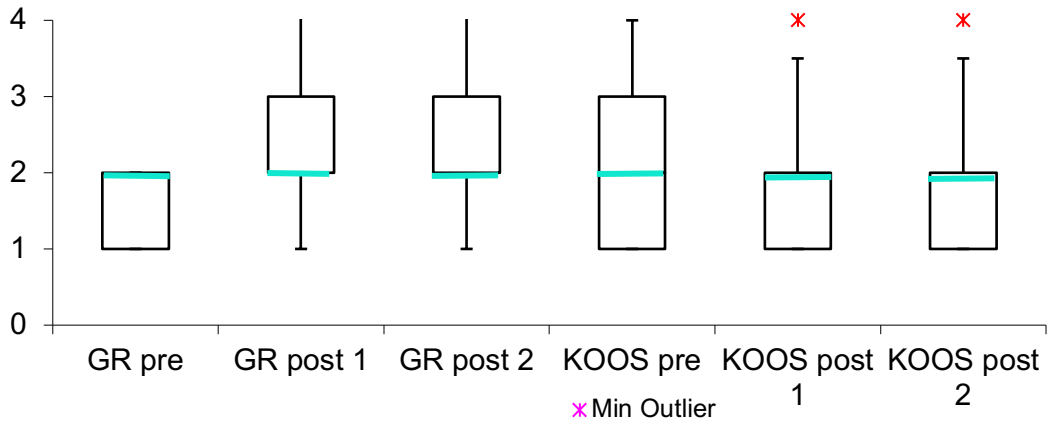


Fig 4. This graphic shows Gardner Roberson hearing class and tumor stage according to Samii and Koos classification remained stable between the first and the final follow-up.

Tables:

RETROSPECTIVE COLLECTED DATA	Patients

Total series:	**22/96 [10]**
Mean Age at GK: Mean Age at last >10 Y	42.5 y.o (median 43, SD 10.9) 56.4 y.o (median 57, SD 9.8).
Male Female	14 (63.6%) 8 (36.3%)
Follow-up	120 and 228 months (mean 167 median of 156 months)
VS volume at GK-SRS	1.2 cm^3 (median 0.6 cm^3, range 0.09–1.7 cm^3, SD 1.5 cm^3)
Marginal radiation dose Mean cochlear dose	13 Gy at isodose 50% 4.7 Gy (median 4.6, SD 1.6)
PRE-GK Samii-Koos	2
LAST 10 Y FU Samii-Koos	2
VS volume at GK-SRS At last FU	1.0 cm^3 (median 0.7 cm^3 SD 1.1).

TABLE 1: Retrospetive collected data of 22 included patients

Audiological assessment	**Patients**
Pre GK hypoacusia	16 (72.7%)
Pre GK Tinnitus	12 (54.5%)
GR I	12 (54.5%)
GR II	10 (45.5%)

Last >10 years FU hypoacusia	21 (95.4%)
GR I	4 (18.2%)
GR II	8 (36.4%)
FU-post GK Tinnitus	12 (54.5%)
Pre –GK GR Class	2
1FU-GK GR Class	3
Last > 10 y GR- GK	2

TABLE 2: Audiological assessment before GK and after more then 10 years of Follow-up. GR: Gardner-Roberson class

DB	PRE-IPISILATERAL-GK	POST-IPSILATERAL GK
250	23.6 dB	42 dB
500	23.6 dB	45.6 dB
1000	30.4 dB	52.2 dB
2000	37 dB	65.6 dB
4000	47.5 dB	77.2 dB

TABLE 3: mean PTA value recorded in ipsilateral VS ear before and at the last follow-up (> 10 years) from GK

DB	PRE-CONTRO-LATERAL-GK	POST- CONTRO-LATERAL-GK

250	18.8 dB	21.2 dB
500	19.3 dB	20.4 dB
1000	20.9 dB	21.6 dB
2000	21.5 dB	26.8 dB
4000	27 dB	36.4 dB

TABLE 4: mean PTA value recorded in controlateral VS ear before and at the last follow-up (> 10 years) from GK

Study	**Sample size (N) and mean length of follow-up**	**Tumors control al last FU**	**Hearing preservation (GR I-II) al last FU %**	**Cumulative hearing preservation rates**	**Conclusions**
Boari et al [10]	96/153 with functional hearing (Audiologicall FU 219 (radiological FU) (mean length of follow-up: 59.9 months)	97.1%	92.6% < 55 years old 42.9% >55 years old	87.8% at 3 years 77.6% at 5 years 75.5% at 10 years in GR Class I 68.1% at 3 years 31.9% at 5 years 21.3%, at 10 years in GR Class II	Younger GR Class I patients had a significantly higher probability of retaining functional hearing even at the 10-year follow up
Kawashima et al [27]	383 (mean length of follow-up: 90-94 months)	90 to 97.3% aged ≤ 40 and > 40 years, respectively	43-44% (aged ≤ 40 and > 40 years, respectively)	63.2% at 3 years 51.1% at 5 years 34.2% at 10 years in the older cohort 74.1% at 3 years 56.0% at 5 years 49.0% at 10 years in the younger cohort	Younger age is non-advantageous for hearing preservation Maintaining long-term hearing function remains challenging due to the influence of irradiation and ischemic, mechanical, or chemical damage to the cochlear nerve
Kawashima [28]	96 (12 Gy cohort with a follow-up period of 124 months 118 >12 Gy cohort with a follow-up period of 143 months.	95% in the 12 Gy cohort 88% in the > 12 Gy cohort	30% 12 Gy cohort 33%>12 Gy cohort	NR	Dose reduction to 12 Gy for GKRS to treat VSs decreased facial and trigeminal nerve complications without worsening tumor control rates.
Hasegawa [29]	440 117 GR I-II (Audiological FU) mean length of follow-up was 38 months	97.5%	47%	55% at 3 years, 43% at 5 years 34% at 8-years	GR hearing class at the time of GKS and the mean cochlear dose affected hearing preservation significantly
Johnson [30]	307 Mean length of follow-up	95%	92.3%	77.8% at 3 years, 68.8% at 5 years, 51.8% at 10 years	Younger patients with smaller tumor volumes reported the best long-term hearing

	was 91.2 months)				preservation rates
Wage et al [31]	112 (Mean length of follow-up was 180 months)	96.9% at 5 years 90.0% at 10years 87.1% at 15 years	40%	66.5% at 2 years, 43.1% at 5 years 37.6% at 10 years	hearing loss correlating with maximum cochlea and modiolus doses
Carlson et al [35]	44 (Mean length of follow-up was 111.6 months)	97.3%	18%	80% at 1 year 55% at 3 years 48% at 5 years 38% at 7 years	Pretreatment hearing capacity and tumor size are jointly statistically associated with time to nonserviceable hearing.
Hasegawa et al [36]	317 (Mean length of follow-up was 93.6 years)	92%	68%13 Gy cohort 13% > 13 Gy	NR	Reduced doses resulted in an acceptable morbidity rate Reduced-dose treatment seems to be as effective as high-dose treatment in tumor control
Tamura et al.[45]	74 (Mean length of follow-up was 55.6 months)	89%	78.4%	In more than 70% of patients, the rate of hearing decrease reaches a plateau after 7 years	patients younger than 50 years are more likely to preserve functional hearing (GR Class 1 and 2) than those older than 50 years hearing preservation being better in the group that received less than 4 Gy to the cochlea hearing decrease at the time of presentation are at risk of functional hearing loss after GK Patients with less lateral extent of the tumor are more likely to maintain functional hearing
Present Series	22 (Mean length of follow-up was 167 months)	100%	54.6%	NR	hearing deterioration occurs especially within 3 years after GKSRS. Hearing function however continues to deteriorate after the first 1-3 years. This decline is not more influenced by aging or pre GK hearing class (GR). suggesting a role of radiation toxicity.

TABLE 5: Summary of data in the literature restricted to a population similar to that included into the study

CHAPTER 4

4.1 Background and study rationale

Patients affected by unilateral VS showed unilateral or asymmetric sensorineural (SN), down-sloping / high frequency hearing loss with speech discrimination decrease. Single-sided deafness (SSD), the unilateral sensorineural deafness in the poorer ear, with normal hearing in the opposite ear, is one of the most common consequences of the growth and therapy of the VS. When functional hearing deteriorations occur, the benefits of binaural hearing are lost. The audiological impact of sporadic VS in patients with normal contralateral hearing is mainly due to the loss of binaural hearing. This comprises a diminished summation effect (identical signal arriving at both ears), a reduction of the squelch effect (ability of the brain to separate noise and speech coming from different locations), and the head shadow effect (speech discrimination when the head is between the source of the sound and the hearing ear). Patients with SSD, have problems in understanding speech in a noisy environment and cannot localize the direction of sounds. The audiological impact of deafness has a significant negative effect on the quality of life in VS patients. The risk of complete hearing loss, either due to the treatment or from the natural course of the disease, requires more effort to provide a satisfactory result but when hearing preservation is not possible, hearing rehabilitation should be considered as an important step to afford quality of life to the patient.

The rehabilitation of patients with single-sided deafness (SSD) or asymmetric hearing loss can be achieved with conventional (bilateral) contralateral routing of signals ((Bi)CROS) hearing aids ((Bi)CROS-HA, (Bi)CROS) or cochlear implants (CI).

Contralateral Routing Of Signals (CROS) and a bi-Cross Hearing Aid are a feasible and non-invasive approach to SSD. The goal of these devices is to obtain two-sided hearing when true bilateral hearing is not possible. Results with these devices are not homogeneous and not easily accepted by patients, possibly because sound information coming from both sides are over imposed on the same ear. Therefore, the CROS device may be considered a pseudo binaural rehabilitation. On the contrary, even if a cochlear implant (CI) requires surgery, it has been effectively used in SSD with promising results such as an improvement in speech comprehension in noise and in sound localization, and partial suppression of subjective incapacitating tinnitus.

The minimally invasive management of VS with GK-SRS results in a low complication rate and good tumor control if compared to surgical or wait and see management.

The preservation of the anatomy of the cochlea and cochlear nerve as appended with radiosurgical treatments can allow hearing restoration and represents a potential for favourable hearing outcomes with CI in sporadic VS.

One topic of discussion is that radiation-induced injury to the cochlear nerve after SRS can compromise the potential for hearing restoration through a CI and that radiosurgery might be disadvantageous for long-term preservation or potential restoration of hearing. To date, only circumstantial evidence exists regarding CIs and radiosurgery or radiotherapy. However, available data show that CIs lead to improved hearing in NF2 patients who have undergone radiation treatment to control their acoustic neuroma.

With the promising results after CI placement in SSD non VS related, interest is increasing in preserving the integrity of the cochlear nerve during VS treatment. In patients with bilateral deafness, hearing loss restoration options are auditory brainstem or cochlear implantation (CI). The deciding factor for CI is based on the presence of a functioning cochlear nerve and blood supply.

If the cochlear nerve can be left intact, the combination of stereotactic radiosurgery followed by a CI might have a significant and positive impact in preserving the quality of life in patients with VS.

In the present chapter is presented a literature review focused on the impact of bilateral deafness in NF2 patients on quality of life (QoF). This study evaluated the possible role of hearing rehabilitation and its impact on QoF in patients with severe bilateral hearing loss.

4.1 The emerging role of hearing loss rehabilitation in patients with vestibular schwannoma treated with gamma knife radiosurgery: literature review.

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Neurosurg Rev. 2021 Feb;44(1):223-238. doi: 10.1007/s10143-020-01257-8. Epub 2020 Feb 6. PMID: 32030543 Review.

Abstract

Stereotactic radiosurgery (SRS) is currently the most common treatment for small to medium-size vestibular schwannoma (VS). Despite favorable outcome, hearing deterioration still remain an underestimated problem and the role of hearing rehabilitation is an under investigated topic. Among available technologies, cochlear implant (CI) should represent a valid alternative in sporadic VS with single side deafness and in Neurofibromatosis (NF2) with bilateral profound hearing loss.
A literature review of the current clinical data was performed searching scientific literature databases.
From all of the articles found, 16 papers were selected. 44 subjects treated with radiosurgery (18 male, 19 female and in 7 cases sex were not specified; 43 NF2 and 1 sporadic VS) were included in the analysis. Epidemiological, clinical, tumor, treatment and audiological data were collected.
Clinical outcome al last follow-up showed an audiological improvement in 25 of the 44 patients. The audiological outcome was unchanged in 16 cases. Audiological deterioration was recorded in 3 cases. Severity of NF2 phenotype, long history of ipsilateral profound deafness before implantation, progressive tumor growth and high radiation dose (20 and 40 Gy) were found in patients with a worst audiological outcome.

Hearing rehabilitation can improve audiological results for VS patients following SRS in selected cases. Hearing rehabilitation with cochlear implant (CI) in SSD leads to partial restoration of binaural hearing with an improvement in speech comprehension in noise and in sound localization, and partial suppression of subjective incapacitating tinnitus

SRS followed by CI, may represent in selected cases a potential emerging option in the management of these patients, aimed to improve their quality of life. Possible implications for the follow-up of these patients are still present, although partially resolved.

Introduction

Vestibular schwannoma (VS) is typically a benign, encapsulated, slow-growing tumor that originates from the vestibulo-cochlear nerve (VIII cranial nerve). VS correspond to approximately 6-10% of all intracranial neoplasms [1]. Most VS are sporadic, but 5-13% are associated with neurofibromatosis type 2 (NF2), a genetic syndrome characterized by bilateral brain vestibular schwannomas (VSs) and a worst impact on a patient's quality of life (QoL). [1].

The management of VS includes: observation microsurgical resection, and radiosurgery or radiotherapy. In NF2 patients, chemotherapy with bevacizumab has also been reported [2]. While microsurgery has been the primary active treatment of VS for many years, together with primary observation [3-6], Gamma Knife stereotactic radiosurgery (GK-SRS) is currently considered a valid and approved alternative for small to medium-size tumors.

Many patients also prefer radiosurgery to surgical resection due to the significantly lower morbidity and mortality rate (0-6%) and similar rates of long-term tumor control (87 to 98.4%) when compared to microsurgical resection [3-14].

Despite the favorable results in term of tumor control, morbidity and mortality rate if compared to surgical excision, hearing deterioration represent the main unresolved drawback of GK-SRS procedure especially for younger patients [7-12]

VS has a natural history of hearing loss, which is caused by a combination of auditory nerve compression and cochlear dysfunction due to ischemia, infarction, or invasion. A common audiometric sign of VS is the progressive speech discrimination decline that is worse than expected for the degree of hearing loss [4,13].

Besides this natural progression, GKSRS post-treatment hearing loss has an unclear and multifactorial pathophysiology also due to the radiation damage [14,13].

Hearing loss resulting from bilateral VSs has a devastating impact on QoL of patients with NF2 [1, 15-17]. Deafness creates a brutal rupture in the patients' course of life that further deteriorates their QoL [1,16-22]. On the contrary, the negative impact on QoL of people with unilateral hearing loss after GK-SRS for sporadic VS is still an underestimated problem [17-

20]. The audiological impact of unilateral deafness in patients with sporadic VS and normal contralateral hearing (single side deafness, SSD) is mainly the loss of binaural hearing, which is a three-dimensional perception needed for good comprehension of speech in noisy environments, localization and orientation to sounds [18]. Patients with substantial unilateral hearing loss report a reduced QoL [20-22]. Analysis of SSQ questionnaires provided great details of how mode of unilateral input differentially influenced listening in a variety of scenarios and contexts, affecting all aspects of daily communication [21-23]. Hearing rehabilitation with cochlear implant (CI) in SSD leads to partial restoration of binaural hearing with an improvement in speech comprehension in noise and in sound localization, and partial suppression of subjective incapacitating tinnitus [20].

Despite many studies describe the possible causes or influencing factors of hearing loss after SRS for VS, only few authors have purposed the use of devises for hearing rehabilitation in VS patients [23-40]. Data concerning CI outcomes in patients after sporadic VS surgical resection are very limited, but promising. In these patients an improvement of speech perception in noise, in sound localization with tinnitus suppression has been observed, showing how CI could be a viable solution [19,20,23].

Data concerning CI outcomes after VS-SRS are described, but are still limited to NF2 patients, and the results are affected by patients' and tumor variables and a correlation with radiation dose and acoustic drops is not possible [25-40].

The aim of the present study was to highlight the impact of hearing loss and the role of hearing rehabilitation after VS-SRS treatment.

A descriptive review of literature was performed in order to define the role of hearing rehabilitation after GKRS treatment in VS patients. Clinical case reports of patients undergoing CI surgery after VS-SRS were collected and analyzed in order to evaluate the audiological outcomes in sporadic and NF2 VS treated by GKRS.

A second aim of the study was to evaluate the possible role of CI in sporadic VS treated with GKRS, establishing a plan for a more evidence-based approach for patients suffering from SSD or deafness.

Materials and methods

A literature review of the current clinical data was performed searching scientific literature databases. Relevant references of published articles were screened. The Medline search was conducted on Pubmed, Scopus, Embase, ISI-web, Cochrane library and Web of Science. Keywords and mesh terms searched were: cochlear implants AND acoustic neuroma; cochlear implant and vestibular schwannoma; cochlear implants AND radiation therapy AND acoustic neuroma; cochlear implants AND radiation therapy AND vestibular

schwannoma; cochlear implants AND radio-surgery, Stereotactic radio-surgery AND cochlear implants; hearing restoration AND radiosurgery.
Articles reporting clinical and audiological outcomes in NF2 patients were included. Case reports, case series, editorials, technical reports, case–control studies, cohort studies, retrospective studies, meta-analyses or clinical trials reporting clinical and audiological outcomes after GKRS treatment were considered. Systematic reviews were thoroughly screened for possible inclusion. Non-English articles and animal studies were excluded. Other exclusion criteria were: papers dealing with GKSRS in VS patients not treated with CI, and with less than five months of follow up (FU); patients with CI in only observed or surgical treatment VS. The search results were independently screened by two of the authors (CM and PM); disagreements were resolved by consensus.
Selected articles reporting CI patients affected by VS and treated with radiotherapy and radiosurgery, the following data were extracted from each article, if reported:
year of publication, number of patients included in each study, number of patients treated with radiotherapy out of the total, epidemiological and demographic data of the patients (gender, age, diagnosis of NF2), preoperative symptoms, time to implantation, median interval between tumor intervention and implantation, the median ipsilateral duration (MO) of deafness before CI, hearing in the contralateral ear at the time of CI, preoperative audiological data (PTA WRS), tumor data (size), tumor treatment (only radiosurgery/radiotherapy or radiosurgery/radiotherapy and surgery), dose of radiation therapy, type of cochlear implant used, complications, average follow up, postoperative clinical, and audiological outcomes.

The collected data were analyzed by means of descriptive statistics (absolute and relative frequencies). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as percentages.

Results

The search of the articles was performed on Pubmed, Scopus, Embase, ISI-web, Cochrane library and Web of Science: the results were superimposable in all search libraries.

The search produced 738 full text papers. The following keywords were used
- cochlear implant AND vestibular schwannoma: 274 papers
- cochlear implants AND acoustic neuroma: 160 papers
- cochlear implants AND radiation therapy AND vestibular schwannoma: 21 papers
- cochlear implants AND radiation therapy AND acoustic neuroma: 19 papers

- Gamma Knife AND cochlear implant: 26 papers
- stereotactic radiosurgery AND cochlear implants: 12 papers
- hearing restoration AND radiosurgery: 3 papers
- hearing preservation after Gamma Knife radiosurgery: 211 papers
- audiological outcome AND Gamma Knife radiosurgery: 13 papers

Literature review results were depicted in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Fig 1).

From all of the articles found, 169 non-duplicate studies were initially selected and 130 articles were excluded.

From the remaining thirty-nine (39) studies, sixteen (16) case reports or case series describing patients affected by sporadic or NF2 VS that underwent CI after VS radiosurgical treatment were selected. Out of a total of 138 patients described in the 16 included papers, 44 subjects were treated with radiosurgery (18 male, 19 female and in 7 cases the sex was not specified; 43 NF2 and 1 sporadic VS) and were included in the analysis.

The median age of the patients (when reported) was 45.4 years (SD +/- 17.2). Audiological data were reported as hearing threshold pure tone audiometry (PTA) (16 studies) in dB or as AAOHNS (American Academy of Otolaryngology-Head Neck Surgery) hearing class ranging from A-D (normal to not-serviceable hearing), speech perception in quiet (12 studies), speech perception in noise with a variable fixed signal/noise ratio (SNR) (14 studies).

In studies where speech in quiet or SNR were assessed, it was uncommon to find description of signal and noise presentation or SN ratio, and therefore outcomes will be generically accounted as pre-post SRS: improvement, deterioration or unchanged hearing outcome (Table 1-4) [25-40].

Tumor dimensions were reported in 14 articles (37 cases). According to Koos grading classification [35] all treated tumors were small to medium-size lesions (≤ Koos T3A-B; 25-30 mm in cisternal diameter). Koos stage T1 (tumor confined to IAC or <10 mm) was described in 5 cases. Koos stage T2-T3A (>10 mm <20 mm in cisternal diameter) was described in 14 patients, and 18 cases were T3A T3B. In 7 cases the tumor size was not reported.

The interval between tumor intervention and cochlear ipsilateral implantation was described in 11 articles (25 patients) and the median time was 71 months.

The median ipsilateral duration of deafness before CI was reported in 13 articles (30 patients) and it was 87.5 months. The hearing in the contralateral ear at the time the CI was

reported in 12 articles was described as complete deafness or profound hearing loss (GR hearing class D).
All patients underwent radiation treatment on the ipsilateral implanted tumor. The dose of radiation therapy was reported in 5 studies (14 patients). Stereotactic radiosurgery with Gamma Knife was performed in 9 patients. In 5 cases fractionated radiotherapy was done.
The mean duration of follow-up after CI was 24.42 months.

Audiological assessment:
Preoperative audiological assessment (PTA, WRS) showed profound or severe-profound hearing loss in all cases. PTA 25-4000 HZ DB was 51 dB in only one case (Sporadic AN). Speech perception in quiet was described in 12 papers (21 cases) and the mean value was 6% (word 0-65%-average 8.3%, sentences 0%); speech perception in noise was reported in 10 papers (19 cases) ranging from 0-36% (average 2.16%).
When described (11 articles), intraoperative telemetry was normal in 13 cases. A poor neural response telemetry (NRT) was recorded in 3 patients and in 2 cases no intraoperative electrode response was detected.
The clinical outcome at the last follow up showed an audiological improvement in twenty-five (25) of the forty-four (44) patients. Among these 25, 24 were NF2 and 1 was the only implanted sporadic VS. The audiological outcomes were unchanged in 16 cases all NF2. Audiological deterioration was recorded in 3 NF2 subjects.
More specifically: post-implant audiological assessment showed an improvement related to PTA dB value in 6 papers (20 patients), a no response in quiet for 13 patients, and no response in noise in 16 cases. WRS was recorded in 18 patients ranging from 0-100% (average 52.1%). The sentence score in quiet was recorded for 26 patients, ranging from 0-100% (average 62.5%). Sentence score in noise was described for seventeen (17) patients, ranging from 0-98% (average 52.04%). Open-set speech perception was tested in nineteen (19) patients: 8 patients recorded good or excellent recognition; no sound perception was defined in 2 patients; only environmental sound or lip reading was recorded for 7 patients; one patient was unable to perform the test. No study evaluated patients' QoL.
In the specific literature, hearing loss after SRS is often classified according to the Gardner-Robertson (GR) hearing scale and modification of the Silverstein and Norell classification in five classes: Class I, good or no hearing deterioration; Class II, serviceable; Class III, non-serviceable hearing; Class IV, poor; Class V, deaf; anacusia or not sufficiently evaluable hearing. Nevertheless, for the purpose of the present study, specific audiological data will be discussed. [41-43].

According to the head and neck classification by the American Academy of Otolaryngology, each GR class is associated to a value of pure tone average threshold (PTA) and to a percentage of speech discrimination (SDS) [43].

GR class 1 correspond to PTA of 30 dB or less with a SDS of 70% or greater.

GR class 2 corresponds to PTA of 30 dB or less with a SDS between 50-69%.

Class 1 and 2 correspond to serviceable functional hearing.

GR class 3 corresponds to PTA ≥ 51 dB but more then 30 dB with a SDS between 5-49%.

GR class 4 corresponds to PTA ≥ 91 dB with a SDS between 1-4%.

In GR class 5 PTA is not testable and SDS is 0%.

Discussion

The present study is a review on CI audiological outcomes in patients treated with GKRS for VSs, experiencing post-treatment deafness. Detailed data concerning long-term hearing function at follow-up appointments (> 5 years) after GKRS are scarce, and hearing preservation remains an underestimated problem [9, 41,53].

In patients affected by unilateral VS, deafness is characterized by unilateral or asymmetric sensorineural (SN), down-sloping/high-frequency hearing loss with decrease of speech discrimination. Single-sided deafness (SSD), the unilateral sensorineural deafness in the poorer ear, with normal hearing in the opposite ear, is one of the most common consequences of the growth and therapy for VS [45-49].

Hearing loss greater than 40 decibels (dB)(GR>2) is considered a disabling hearing impairment [43].

When functional hearing deteriorations occur, the benefits of binaural hearing are lost. The audiological impact of sporadic VS in patients with normal contralateral hearing is mainly the loss of binaural hearing, which induces decreased audibility, worsening of perception in noisy environments, of orientation to sounds, and localization of target signals [20-22].

The effects of unilateral hearing loss are: the loss of summation effect (binaural loudness summation, which increases the audibility of a target signal), the reduction of the squelch effect (the ability of the brain to separate noise and speech coming from different locations), and the loss of the head shadow effect (improved speech discrimination in the shielded ear when the head is between the source of the sound and the noise).

The mechanisms of hearing deterioration after radiosurgery for VS are not yet fully understood [46-49] On one side there is a compressive effect on the cochlear nerve, a vascular occlusion of internal auditory artery or vasa nervorum, and the biochemical alterations of the inner ear fluids [45] to the other side radiation is a plausible explanation to hearing loss [45-49,54]. Radiation dose to the cochlea has been proposed as a key

prognostic factor in hearing preservation following SRS and higher radiation dose and larger irradiated cochlear volume are significantly associated with higher risk of hearing loss [49,54]. Therefore, dosimetric parameters like marginal (<13 Gy) and modiolous (<4 Gy) are associated with higher serviceable hearing preservation [51-58].

Hearing deterioration within 3 years after GKRS could be explained by ischemic or mechanical damage to the cochlear nerve due to dose irradiation or nerve compression by transient tumor expansion. This transient tumor expansion can be observed during the first 2 years after treatment, and is a consequence of post-actinic citotoxical edema [9]. Even if in the first 2 years after treatment the mean PTA loss is higher (7.03 dB/year), as has been demonstrated in many articles that hearing acuity continues to deteriorate even beyond 5 years (2.39 dB/year) corresponding with hearing preservation rates of 47–77% at 3 years, 28–64% after 5 years and 23–45% at 10 years [9,51, 59,61]

The causes of this progressive hearing deterioration at long-term follow-up are not known [9].

It seems likely that improvement after CI in SRS treated patients could also be conditioned by different variables such as radiotherapy modality, dose and pre-treatment audiological characteristics of patients [9,51-61]. Therefore, a synthetic overview of SRS effects on hearing is given.

The role of GKRS in VSs and hearing outcomes

Since the first VS radiosurgical treatment in 1979 [50], many studies have investigated and described GKRS as an effective and safe treatment. Actually, many patients prefer radiosurgery to resection because of lower morbidity and shorter hospitalization length compared to surgical resection [9-10, 51-52].

The maximal inner dose should vary from 20 to 32.6 Gy (median 26 Gy), the marginal dose from 11 to 15 Gy (median ≤ 13 Gy). According to some authors the maximum cochlear dose should not exceed 4 Gy to ensure hearing preservation [55]. The isodose line for the tumor margin varied from 40-60% (on average 50%). The number of isocenters can vary from 1 to 41 (on average 12). The application of a low-dose irradiation (marginal dose 11–13 Gy at 50% isodose line), results in 89–99% overall tumor control rates (93–95% at 5 years and 86–95% at 10 years after GKS) [9, 56-58]. The use of lower margin doses (≤ 13 Gy) with a median mean cochlear dose of 4.0 Gy should reduce the risk of cochlear damage but tumor control can be achieved with longer follow up [9, 56-58]. Among the effects on hearing loss, no significant differences between single and fractionated doses are reported in the literature [59-60].

Many investigators have reported relatively long-term hearing outcomes after SRS, but these results are still unsatisfactory, showing an overall serviceable hearing preservation rate of ≤ 50% over longer periods. [9, 46]

The use of conformal and selective irradiation with avoidance of excessive irradiation of the adjacent structures minimizes the risk of treatment-related complications, including trigeminal and facial neuropathy [14].

Many factors, including a patient's age, Gardner-Robertson hearing class before irradiation, Koos tumor stage, extension of the intrameatal part of the neoplasm up to fundus, tumor shape, nerve of tumor origin, presence of cystic changes in the neoplasm, cochlear dose, marginal dose or treatment modality (single section or fractionated), were widely investigated, but only a small amount of data are statistically significant [9, 46-52, 57-61] (Table 5). Nevertheless, hearing deterioration represents the main unresolved drawback of its procedure especially in younger patients [60-61].

CI rehabilitation in SRS treated VS

As mentioned above, a worst Gardner Robertson hearing class before irradiation (GR>2) can be considered as a possible predictor of hearing deterioration after SRS [9, 46-52, 57-61].

When hearing preservation is not possible and hearing deterioration occurs with loss of serviceable hearing (GR>2<5), hearing rehabilitation may provide a better QoL for these patients.

In patients affected by sensorineural hearing loss with retro-cochlear pattern such as in VS, the conventional hearing aid amplifications are often ineffective and auditory brainstem implants (ABI) infrequently permit high-level open-set capacity [26]

Even if the CI was considered a contraindication in sensorineural hearing loss due to retro-cochlear lesions favorable hearing outcomes in NF2 patients have been reported [26, 62-71] since the first case in 1999 [66].

When bilateral severe/profound hearing loss following VS treatment occurs in NF2, CI is indicated to restore, support communication and improve the QoL [1, 15, 19,20].

CI has been performed in NF2 patients even in the presence of asymmetric hearing loss with substantial hearing on one side. In these subjects CI is indicated to support binaural hearing, to maintain residual cochlear nerve stimulation and to minimize hearing deprivation [72].

In NF2 patients CI is mainly proposed when cochlear nerve remains intact, as in presence of a stable tumor after SRS or after nerve preserving surgery [30-32,34,62-71].

A favorable outcome (in squelch effect and sound localization) was also reported in patients with sporadic VS in the only or better hearing ear, with similar results to those patients without VS treated with CI [70].

Patients with substantial unilateral hearing loss report a reduced QoL [22]. Analysis of SSQ questionnaires provided great details of how mode of unilateral input differentially influenced listening in a variety of scenarios and contexts, affecting all aspects of daily communication [24]. The greatest difficulties involved speech in the presence of noise, situations of multiple speech-streams and switching (such as listening to someone speaking and the television at the same time), the location of unseen objects, and increased listening effort ($P < .05$) [73].

One might argue that patients who are more prone toward GKRS with a serviceable hearing on one side, would not consider CI surgery despite it is considered a safe and relatively short procedure, lasting less than 60 minutes both in general and local anesthesia [74]. As a matter of fact, rehabilitation of SSD, beside CI, can be addressed with different audiological approaches such as CROSS systems and the Bone Anchored Hearing Aids (BAHA). Both hearing devices only overcome the head shadow effect, accomplishing a pseudo-binaural hearing. The conventional CROS devices reroute the input signal over the only hearing ear and comprise a microphone placed near the impaired ear and an amplifier (hearing aid) near the normal ear. It only transmits the frequencies of above 1,000 Hz, which results in a ''tinny'' sound. The acceptance is mainly linked to contralateral hearing level and when this last is within normal limits, the success rate is very low: 8.3% [75]. The BAHA system requires osteointegration and, therefore, surgery for placement of the implantable transducer on the squama temporalis, behind the ear. The external speech processor is held in place by a magnet. As for the CI, it presents artifacts occurring during the MRI images acquisition. Despite a better hearing outcome if compared to CROSS due to a larger frequency range, it only improves hearing in the shielded ear, which requires patients to voluntarily orientate the head position in the auditory scenario. Conversely, localization of sounds is usually poor, and the acceptance of surgery <25% of eligible candidates [76]. On the contrary, CI rehabilitation in SSD leads to restoration of binaural hearing with a variable improvement in speech comprehension in noise and in sound localization [21]. It has been reported that 2/3 patients showed significantly better CNC (Consonant Nucleus Consonant) scores in the bilateral condition than solely the normal hearing ear alone, while localization improved in almost 100% patients [77] Furthermore, the suppression of incapacitating tinnitus, which is a unique effect linked to CI stimulation [21], is a result which has significantly improved the QoL of SSD patients, and with appropriate counseling could lead GKSRS SSD subjects to a greater acceptance of surgery.

From the present literature review it emerged that the role of hearing rehabilitation (CI) can improve audiological results for VS patients treated with GKSRS in NF2. Improvements were described ranging from changes in awareness of sounds, lipreading in bilateral NF2,

to open set words, and sentence recognition under noise competition. A general analysis of data reported in the included studies, showed that after a mean follow up of 24.42 months from CI, 56.8% of patients improved audiologically, 36.4% were unchanged and only 6.8% deteriorated. However, due to differences in audiological test items (phonemes, words, sentences) and procedures (i.e. speech in quiet versus noise, lipreading versus open set speech perception), and due to the small numbers of patients implanted, it was not possible to perform a statistical analysis.

More in depth, the case series included reported 45.5% of PTA hearing improvement. Most of these subjects were NF2 patients with bilateral audiological deterioration. In these patients the CI has the main role of rehabilitating one-side hearing prior to the loss of contralateral hearing. Speech perception outcomes showed an improvement in 45.5% of cases, while only thirteen (13) reports have described an improvement of speech perception in noise. 4 patients had serviceable hearing in the contralateral ear, (one of them had bilateral CI) and in these cases could have been analyzed as quasi-SSD. A descriptive analysis of the pool of patients without audiological improvement (36.4% unchanged and 6.8% deteriorated: 43.2% of the total) after a mean follow up of 24.42 months from CI implant showed that the most relevant influencing factors of negative outcome were: severity of NF2 phenotype, long history of ipsilateral profound deafness before implantation, progressive tumor growth after SRS (necessitating surgical resection with resultant cochlear nerve sacrifice and CI removal) and high radiation dose (20 and 40 Gy).

As reported above, CI in SSD patients (4 patients: P23,27,28,29) has the role of restoring binaural hearing; 3/4 subjects showed an audiological improvement. The only patient that remained unchanged (in Carlos. 2016 series [35]) presented a long history of profound hearing loss before implant (Preoperative Word score and sentences score: 0%), and the intraoperative NRT was absented. It is interesting to note, how in none of these patients the role of CI in binaural hearing has been assessed. Conversely, the advantage of binaural hearing as opposed to pseudo binaural one was clearly assessed by Arndt and coauthors [77]. These Authors showed that CI improves hearing abilities in people with SSD and is superior to the alternative treatment options. Furthermore, their data suggested that the binaural integration of electric and acoustic stimulation is possible even with unilateral normal hearing.

Summarizing the present findings, it might be inferred that CI could represent a potential option to recover the severe/profound hearing loss in subject treated with GKSRS, where conventional hearing aids cannot be applied successfully. This is particularly true in NF2 VS. Patients with NF2 who are deaf or have significant hearing loss face numerous and unique challenges which lead to poor quality of life: social isolation, low social support,

tinnitus. Not surprisingly, among all patients with NF, those with NF2 and significant hearing loss or deafness experiences report the lowest quality of life [78].

Few sporadic VS with SSD have been treated up to now, but good hearing restoration is promising as possible therapeutical approach to deafness especially in presence of variable degree of hearing loss in the contralateral ear. Although in a lesser degree, patients with substantial unilateral hearing loss report a reduced QoL, which affect all aspects of daily communication [22, 24].

In all cases the primary indication to CI should be considered in patients with an anatomically preserved cochlear nerve.

If the nerve remains functionally intact with preservation of its anatomy and blood supply (noted by minimal residual hearing at audiogram test), in selected cases CI could represent a possible alternative to other implants. When the cochlear nerve remains anatomically intact after SRS, the CI can still be partially effective also in the presence of acoustic nerve atrophy. As a matter of fact, 81.25% of intraoperatively tested subjects showed a neural response to electric stimulation through the implant [26,29,33,36,38]. The interest in preserving the integrity of the cochlear nerve is increasing in VS treatment, both during surgical [65,79] removal as well as after SRS, and CI could represent a valid option in the perspective of future hearing rehabilitation.

Finally, one more issue must be considered, which is the need of frequent MRI scans during post GKRS radiological follow-up. Sporadic VSs require MRI (usually 1.5Tesla) at 6 months after the first treatment and then every year for 5 years. After 5 years, MRI can be obtained every 2 years.

Conversely NF2 patients require a lifelong radiological surveillance and in these patients hearing might bilaterally deteriorate really fast [80].

In the past the magnetic components of the CI were considered a contraindication to MRI because of possible image artifacts and limitation of diagnostic validity. Therefore, devices with removable magnets were routinely introduced. Magnet removal, although easily performed via a small skin incision under local anesthesia, should be avoided when possible, because the procedure may lead to additional discomfort for the patient and to an increased risk of possible complications (scars, adhesions, infections).

More recently, safe and successful MRI scans without magnet removal has been reported in 1.5 Tesla MRI in retrospective series [80].

Moreover, post 2016 manufactured devices with non-removable magnets were approved for 3 Tesla MRI with no risks of pain or discomfort for the patients [81].

Sequences such as FIESTA (fast imaging employing steady-state acquisition) or 3D inversion recovery-prepared fast spoiled gradient echo (IR-FSPGR) followed by coronal and

axial sections have been studied to improve the IAC and cerebellopontine angle (CPA) visualization both ipsilateral and contralateral to CI housing. MRI scanning without magnet removal actually could be safer than before and better tolerated procedure in patients with auditory implants [80- 82-83].

A further solution could be a more horizontal and posterior surgical positioning of the magnet, which has been proposed to allow better visualization of the IAC and the labyrinth, making CPA visualization possible [84].

There are numerous limitations inherent within our study. The study is a descriptive review of the literature and the included cases lacked validated outcome measures. The patients' population is heterogeneous and the radiosurgical treatment modality and parameters are not reported in all papers. The number of collected patients is limited. The lack of a consistent cohort of sporadic VS patient did not allow us to establish a control group for comparison.

Conclusion

The negative impact on a patient's QoL from hearing loss after Gamma Knife for VS is still an underestimated problem, and the role of hearing rehabilitation is an under investigated topic especially for those patients with bilateral or unilateral severe/profound hearing loss. Data concerning CI outcomes in VS patients (sporadic and NF2) treated with SRS are promising. Therefore, radiosurgery followed by CI when indicated, may represent a potential emerging option in the management of these patients, aimed to improve their QoL. A possible relation between factors influencing hearing drops after SRS, and the implantation timing has not yet been comprehensively investigated.

To date the time of implantation depends on the level of sentence recognition reduction (50%) related to the level of stimuli (in dB), and hearing deterioration can happen both in the early stages after treatment or at long-term follow up.

Radiological follow up with periodic MRI may represent a disadvantage for implanted patients, but the related problems have been investigated and partly resolved. An important open question is related to the radiological follow-up in patients with early hearing loss, but related data in the literature is still poor. Despite the current state of minimal data and the possible complications and implications for the follow-up of the patients after CI surgery, these results are promising; therefore a plan for a more evidence-based approach to this complex scenario could be advisable.

Conflict of interest

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article. The Authors declares that there is no conflict of interest

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FIGURES:

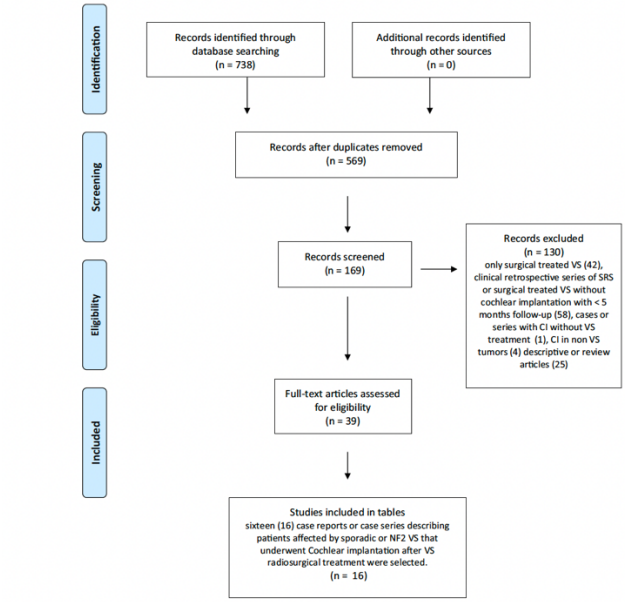

Fig. 1 PRISMA flow diagram

Fig. 1 PRISMA flow diagram

TABLES:

Table 1 Subjective and audiological characteristics of subjects with sporadic acoustic neuroma (AN) or neurofibromatosis (NF2) treated with SRS (stereotactic radiosurgery).

Author	CI-SRS-VS	Sex	Age	NF2/AN	Median interval between tumor intervention and implantation (months)	The median ipsilateral duration (months) of profound hl before CI	Hearing in the contralateral ear at the time of CI	VS size (cm^3)	Radiation dose (Gy)
Amoodi et al. [25]	P1	F	26	NF2	NR	96	Profound HL	3	NR
Carlson et al. [26]	P2	M	50	NF2	22	1	Profound HL	1.4	Margin, 13; max, 26
	P3	M	61	NF2	12	2	Profound HL	1.1	Margin, 15; max, 30
	P4	F	44	NF2	24	235	Profound HL	IC	Margin, 20; max, 40
	P5	M	37	NF2	177	179	Profound HL	1.4	Margin, 16; max, 32
Lustig et al. [27]	P6	F	41	NF2	NR	41	Profound HL	NR	NR
	P7	M	50	NF2	NR	22	Profound HL	NR	NR
Mallory et al. [28]	P8	NR	Group	NF2	Group median score 91.2	Group median score 169.2	NR	Group	Median marg 14 max 28
	P9	NR	medi-	NF2			NR	median	
	P10	NR	an 37	NF2			NR	score 2.7	
	P11	NR		NF2			NR		
Trotter and Briggs [29]	P12	M	52	NF2	72	60	Profound HL	NR	54 Gy (30 fractions) at the 90% isodose line
	P13	F	41	NF2	84	NR	Profound HL	3	50.4 Gy in 28 fractions to the 90% isodose
	P14	M	84	NF2	12	NR	Profound HL	NR	12 Gy prescribed to the 87% isodose in a single fraction
ROEHM et al. [30]	P15	F	60	NF2	120	120	NR	2.5	NR
Tran Ba Huy et al. [31]	P16	M	26	NF2	24	24	Profound HL	KOSS2	NR
Lassaletta et al. [32]	P17	F	27	NF2	NR	NR	Hearing class D	2.5	NR
	P18	F	24	NF2	NR	NR	Hearing class D	2.5	NR
Harris et al. [33]	P19	F	54	NF2	156	204	NR	1.3	NR
	P20	M	64	NF2	228	240	NR	1.1	NR
	P21	M	80	NF2	24	12	NR	2.7	NR
	P22	F	41	NF2	192	96	NR	2.3	NR
	P23	M	64	NF2	192	168	Residual natural hearing	2.2	NR
	P24	M	44	NF2	168	120	NR	2.1	NR
Costello et al.[34]	P25	F	57	NF2	12	120	Profound HL	KOSS1	NR
Carlson et al. [35]	P26	M	36	NF2	NR	10	Profound HL	1.5	Marginal dose of 13 Gy, 26 max
	P27	M	52	NF2	NR	120	75 SRT/20% WRS	1.4	5040 cGy in 28 fractions
	P28	M	54	NF2	NR	84	Previously implanted	0.5	5040 cGy in 28 fractions
	P29	M	37	NF2	NR	180	60 SRT/50%	1	Marginal dose 16, 32 max
Mukherjee et al. [36]	P30	M	44	NF2	12	NR	Profound HL	1.5	NR
	P31	F	55	NF2	12	96	Profound HL	1.3	NR
	P32	F	72	NF2	12	24	Profound HL	IAC	NR
	P33	F	26	NF2	12	12	Profound HL	1.9	NR
	P34	F	18	NF2	12	6	Profound HL	2.3	NR
	P35	F	20	NF2	12	72	Profound HL	3.7	NR
Pisa et al. [37]	P36	M	77	NF2	NR	65	Profound HL	0.1	12.5 GY 50%
	P37	F	38	NF2	NR	26	Profound HL	3	12.5 Gy

Table 1 Subjective and audiological characteristics of subjects with sporadic acoustic neuroma (AN) or neurofibromatosis (NF2) treated with SRS (stereotactic radiosurgery).

Table 1 (continued)

Author	CI-SRS-VS	Sex	Age	NF2/AN	Median interval between tumor intervention and implantation (months)	The median ipsilateral duration (months) of profound hl before CI	Hearing in the contralateral ear at the time of CI	VS size (cm^3)	Radiation dose (Gy)
									50% isodose
Tan et al. [38]	P38	F	36	NF2	96	96	Profound HL	NR	NR
	P39	F	20	NF2	6	12	Profound HL	NR	NR
Peng et al. [39]	P40	M	40	NF2	NR	NR	NR	2	NR
	P41	F	20	NF2	60	NR	NR	3	NR
Pai et al. [40]	P42	NR	36	NF2	NR	NR	NR	NR	NR
	P43	NR	42	NF2	NR	NR	NR	2	NR
	P44	NR	76	AN	NR	NR	NR	2.3	NR

Hearing loss (HL) is reported with a variable classification, ranging from average PTA in dB to AAOHNS (American Academy of Otolaryngology–Head and Neck Surgery) hearing class ranging from A–D (D = unserviceable hearing); *SRT*, speech reception threshold; *NR*, not reported

Table 1 Subjective and audiological characteristics of subjects with sporadic acoustic neuroma (AN) or neurofibromatosis (NF2) treated with SRS (stereotactic radiosurgery).

Table 2 Pre-operative audiological data and intraoperative neural telemetry

Author	CI-SRS-VS	Audiological assessment (open set)[1]	PTA dB[2] 250–4000 Hz	Speech perception quiet[3]	Speech perception noise[4]	Intraoperatory neural telemetry AT CI electrodes[5]
Amoodi et al. [25]	P1	Hint sentences recognition, CNC word test	≥90	Words 48% 90 dB HL (right) no response on left	NR	NI
Carlson et al. [26]	P2	CNC words, CUNY, AzBio sentences, BKB-SIN	≥90	NR	NR	NI
	P3					NI
	P4					Poor NT
	P5					Poor NT
Lustig et al. [27]	P6	Words, hint	≥90	0%	NR	NR
	P7					
Mallory et al. [28]	P8	Hint, monosyllabic words recognition	≥90	NR	NR	NR
	P9					
	P10					
	P11					
Trotter and Briggs [29]	P12	CUNY, sentence score in quiet, CNC words	≥90	NR	NR	NI
	P13					No NT
	P14					No NT
Roehm et al. [30]	P15	CNC word, CUNY, hint	Profound SNHL	0%	0%	NI
Tran Ba Huy et al. [31]	P16	Open-set words and sentences	≥90	0%	0%	NI
Lassaletta et al. [32]	P17	Dissyllabic word recognition	≥90	0%	0%	NR
	P18					
Harris et al. [33]	P19	BKB sentences, CUNY sentences	≥90	0%	0%	NI
	P20			0%		NR
	P21			0%		NR
	P22			0%		Poor NT
	P23			0%		NR
	P24			36%		NR
Costello et al. [34]	P25	CUNY	≥90	0%	0%	NR
Carlson et al. [35]	P26	Words, CNC, AzBio	85	32% CNC	36% AzBio	NR
	P27		≥90	0%	0%	
	P28		≥90	0%	0%	
	P29		0	0%	0%	
Mukherjee et al. [36]	P30	BKB, CUNY, lip reading	≥90	0%	0%	4 PT NI
	P31					
	P32					
	P33					
	P34					
	P35					
Pisa et al. [37]	P36	CNC words, CUNY, AzBio sentences and hint in noise test	≥90	0%	0%	NR
	P37			2%	3%	
Tan et al. [38]	P38	Words	≥90	0%	0%	NI
	P39					NI
Peng et al. [39]	P40	NU chips, Iowa and CUNY	NR	NR	NR	NR
	P41					
Pai et al. [40]	P42	CUNY, BKB	≥90	NR	0%	NR
	P43		≥90	0%		
	P44**		51	9% CUNY		

*2 subjects, 1 bilateral CI; **sporadic AN

[1] Speech perception assessment: it varies going from consonant and vowel recognition to word and sentence recognition in quiet and in noise. In few subjects, open-set recognition was not measurable for poor perception outcome, but still patients had detection of sounds, which supported lip reading and it was reported as an improvement

[2] When reported ≥ 90 dB from 250 to 4000 Hz: profound or severe-profound hearing loss

[3] Open-set speech perception (when reported) = words 0–65% (average 8.3%) sentences 0%

[4] Open-set speech perception (when reported) = 0–36% (average 2.16%)

[5] NT AT CI electrodes: *NI* nerve integrity, *NT* neural telemetry, *NR* not reported

Table 2 Pre-operative audiological data and intraoperative neural telemetry

Table 3 Post-operative hearing is reported with variable classification, ranging from average PTA in dB to AAOHNS hearing class ranging from A to D

		Post-implant audiological assessment (FU)						
Author	CI-SRS-VS	PTA DB	SP quiet no response	SP noise no response	Word score	Sentence scores in quiet	Sentence scores in noise	Benefit in patients without open-set recognition
Amoodi et al.[25]	P1	NR	NR	NR	52% AT	94% AT	NR	NR
Carlson et al. [26]	P2	18	2 PT	3 PT	46% CNC	100% CUNY, 95% hint	NR	OSP
	P3	20			86% CNC	95% AzBio	9.75 dB BKB-SIN	OSP
	P4	19			NR	NR	NR	OSP
	P5	NR			NR	NR	NR	No sound perception
Lustig et al. [27]	P6	55	NR	1	46% mWRS	NR	NR	Awareness of sounds and better lip reading
	P7	35	NR	NR	NR	46% SDS	98% hint	Excellent
Mallory et al. [28]	P8	Hearing class: A-D	NR	NR	46% mWRS	NR	95% hint	OSP
	P9				NR	NR	NR	OSP
	P10				86% CNC	95% AzBio		OSP
	P11				NR	NR	NR	NO SOUND PERCEPTION
Trotter and Briggs [29]	P12	NR			79% CNC	96% CUNY	79% CUNY	NR
	P13			1	45% CNC	72% CUNY		NR
	P14				NR	NR	NR	ESA, LP
Roehm et al. [30]	P15	NR	NR	NR	NR	92–90% CUNY	58% hint	NR
Tran Ba Huy et al. [31]	P16	NR	NR	NR	100% mWRS	96%	91%	NR
Lassaletta et al. [32]	P17	Hearing class: D	1	1	NR	NR	NR	NR
	P18		1	1				
Harris et al. [33]	P19	≥30 dB				82% BKB	54% BKB	
	P20	≥35 dB				100% BKB	86%BKB	
	P21	≥35 dB	1	1				
	P22	≥35 dB	1	1	28%			
	P23	≥25 dB				90%BKB	26 %BKB	
	P24	≥30	1	1	56%			NR
Costello et al. [34]	P25	NR	NR	NR	NR	36% CUNY	NR	NR
Carlson et al. [35]	P26	25 dB	NR	NR	88% CNC	90% AzBio	NR	NR
	P27	28 dB	NR	NR	42% CNC	73% AzBio	NR	NR
	P28	22 dB	NR	NR	50% CNC	72% AzBio	NR	NR
	P29	NR	NR	NR	0	0	NR	NR
Mukherjee et al. [36]	P30	NR	1	1	NR	0%	0%	LP
	P31	NR	-	-	NR	82% BKB	54% BKB	
	P32	NR	1	1	NR	0%	0%	ESA
	P33	NR	1	1	NR	0%	0%	LP
	P34	NR	1	1	NR	NR	NR	LP
	P35	NR	1	1	NR	NR	NR	LP
Pisa et al. [37]	P36	22 dB	NR	NR	28% WRS 28% CNC WORD	NR	34% HINT	

Table 3 (continued)

		Post-implant audiological assessment (FU)						
	P37*	25 dB (L-R)			52 AND 8% WRS (L-R) 40 and 24 %CNC word (L-R)	NR	45% hint (L-R)	
Tan et al. [38]	P38	80 dB			0 mWRS 5 dWRS 5 SRS	5%	NR	ESA, LP
	P39	25 dB			60 mWRS 78 dWRS 82 SRS	60%	NR	OSP
Peng et al. [39]	P40		1	1	NR	NR	NR	NR
	P41					87% CUNY		
Pai et al. [40]	P42	NR	NR	NR	NR	NR	NR	NR
	P43	30 dB	NR	NR	NR	63% BKB	94% CUNY	NR
	P44**	36 dB	NR	NR	NR	0% BKB	61% CUNY	NR

*Single patient with two implanted ears. **Sporadic acoustic neuroma. *CI* cochlear implant, *PTA* pure tone audiometry, *mWRS* monosyllabic word recognition score, *dWRS* disyllabic word recognition score, *SRS* sentence recognition score, *CNC* Consonant Nucleus Consonant test words, *OSP* open-set speech perception, *ESA* environment sound awareness, *LP* lip reading, *BKB* Bamford-Kowal-Bench, *CUNY* City University of New York, *AzBio* Arizona State University Sentence Test, *SP* speech perception

Table 3 Post-operative hearing is reported with variable classification, ranging from average PTA in dB to AAOHNS hearing class ranging from A to D

AUTHOR	CI-SRS-VS	FU (months)	AUDIOLOGICAL OUTCOME (IMPROVED, UNCHANGED, DETERIORATED)
Amoodi et al. [25]	P1	12	Improved
Carlson et al. [26]	P2	22	Unchanged
	P3	56	Improved
	P4	25	Deteriorated
	P5	12	Deteriorated
Lustig 2006 [27]	P6	17	Improved
	P6	18	Improved
Mallory et al. [28]	P8	30	Unchanged
	P9	12	Deteriorated
	P10	60	Improved
	P11	NR	Unchanged
Trotter and Briggs [29]	P12	36	Improved
	P13	12	Improved
	P14	NR	Improved
Roehm et al. [30]	P15	32	Improved
Tran Ba Huy et al. [31]	P16	48	Improved
Lassaletta et al. [32]	P17	44	Unchanged
	P18		Unchanged
Harris et al. [33]	P19		Improved
	P20	60	Improved
	P21		Unchanged
	P22		Unchanged
	P23		Improved
	P24	6	Unchanged
Costello et al. [34]	P25	12	Improved
Carlson et al. [35]	P26	2	Improved
	P27	25	Improved
	P28	4	Improved
	P29	3	Unchanged
Mukherjee et al. [36]	P30	12	Unchanged
	P31	12	Improved
	P32	6	Unchanged
	P33	6	Unchanged
	P34	NR	Unchanged
	P35	NR	Unchanged
Pisa et al. [37]	P36	12	Improved
	P37	12	Improved
Tan et al. [38]	P38	20	Improved
	P39		Improved
Peng et al. [39]	P40	81.6	Unchanged
	P41		Improved
Pai et al. [40]	P42	3	Unchanged
	P43	9	Improved
	P44(AN)*	12	Improved

*AN sporadic acoustic neuroma

Table 4 Descriptive audiological outcome at last follow up

Table 5 Most relevant parameters that can predict the probability of hearing preservation after GKRS

Factors influencing hearing outcome after radiosurgery	Main results in the literature	Significant variables
Patient's age	≥ 55 years had a higher probability of losing serviceable hearing	• Univariate regression analysis [52, 54] • Multivariate analysis [9]
Gardner-Robertson hearing class before irradiation	GR > 2 worst outcome	• Univariate regression analysis [9, 54] • Multivariate regression analysis [51, 54]
Koos tumor stage	Tumor volume and its morphology	• Univariate regression analysis [51, 54] • Multivariate regression analysis [45–48]
Extension of the intrameatal part of the neoplasm up to fundus	IAC involvement Pear and linear tumor shape	• Multivariate analysis [9, 45, 48]
Median cochlear dose	< 4 Gy	• Univariate regression analysis [53] • Multivariate analysis [51, 53]
Marginal dose 11 to 15 Gy (median ≤ 13 Gy)	Marginal dose < 13 Gy	• Univariate regression analysis [46, 51]

Table 5 Most relevant parameters that can predict the probability of hearing preservation after GKRS.

APPENDIX

In this section were includes the following articles:

1-Cranioplasty with Porous Hydroxyapatite Custom-Made Bone Flap: Results from a Multicenter Study Enrolling 149 Patients Over 15 Years
This study was aimed to value the incidence of adverse events and implant removal in Porous Hydroxyapatite Custom-Made Bone Flap.
Marco Fricia1, Federico Nicolosi2, Mario Ganau3, Helene Cebula3, Julien Todeschi3, Marie des Neiges Santin3, Benny Nannavecchia3, Carlotta Morselli2, Salvatore Chibbaro3
Original article
World Neurosurg. 2019 Jan;121:160-165

2-Comparison between the different types of heterologous materials used in cranioplasty: a systematic review of the literature
This study was aimed to examine the association between material of choice and related complications to suggest the best treatment option.
Carlotta MORSELLI [1, 2], Ismail ZAED [1] *, Maria P. TROPEANO [1], Giovanni CATALETTI [1], Corrado IACCARINO [3], Zefferino ROSSINI [4], Franco SERVADEI [4]
Originale article
J Neurosurg Sci. 2019 Dec;63(6):723-736.

3-Arthrogenic human synovial cysts: immunohistochemical profile of IL-1β, IL-6, TNF-α
This study based on histological results supposed inflammatory cytokines as IL-1β, IL-6, TNF-α may have a significant role in the pathogenesis and regression of synovial cysts.
Authors: S. Taurone, M. T. Santarelli, C. De Ponte, L. Bardella, M. Ralli, C.
Morselli, A. Nicolai, A. Greco, A. Ferretti, M. Artico

4-Management of Gunshot wound to the lumbosacral spine in a 17-year-old girl without neurological impairment. Case description.
This case report describes the surgical removal of retained bullet into the spinal canal
[1]Bassani Roberto, Morselli Carlotta[1,2]
Case report
J Biol Regul Homeost Agents.
2020 Jul-Aug;34(4 Suppl. 3):1-5.
Congress of the Italian Orthopaedic Research Society.

5-Congenital instability of cervical spine in a pediatric patient with cleft lip and palate

Carlotta Morselli [1,2], Patrizia Mancini [3], Agostino Cirullo [4], Laura Mangiavini [1,5], Roberto Bassani [1].

Our reference: INAT 101413

Article reference: INAT_INAT-D-21-00371

Accepted in: Interdisciplinary Neurosurgery: Advanced Techniques and Case Management

5.1 Cranioplasty with Porous Hydroxyapatite Custom-Made Bone Flap: Results from a Multicenter Study Enrolling 149 Patients Over 15 Years

Marco Fricia1, Federico Nicolosi2, Mario Ganau3, Helene Cebula3, Julien Todeschi3, Marie des Neiges Santin3, Benny Nannavecchia3, Carlotta Morselli2, Salvatore Chibbaro3

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Original article
World Neurosurg. 2019 Jan;121:160-165

Abstract

BACKGROUND: Despite the mixed evidence regarding the effect of decompressive craniectomy in terms of outcome, a tremendous increase in related reports has been observed in the last years. Cranioplasty plays a key role in restoring function and anatomy of the cranial vault. Considering that cranioplasty is not exempt from risks, the identification of the safest technique becomes crucial to achieve better patients' recovery. Porous hydroxyapatite (PHA) has received growing attention for its potential in bony integration. Here we report a multicenter prospective follow-up analysis of 149 patients who underwent cranioplasty with PHA prostheses. In particular, we focus on the incidence of adverse events and implant removal.

METHOD: From January 2001 to December 2015 we conducted a prospective multicenter study of 149 patients who underwent cranioplasty with custom-made PHA flaps after decompressive craniectomy for several reasons. The endpoints were the incidence of adverse events after cranioplasty and of related implant removal.

RESULTS: 66 patients (44%) were treated within 6 months from decompression, and only 2 patients had a bifrontal bilateral reconstruction. Of those, 25 patients reported complications (16.8%), and 9 of them (6%of the whole case series) required removal of the prosthesis. The only significant factor predicting cranioplasty removal was a previous infection.

CONCLUSION: Hydroxyapatite for cranial implants is fully comparable to other heterologous materials. It has a biologic potential of bony integration. The risk of explants seems to be significantly higher in second-line patients, data not shown in previous studies.

Introduction

In 2007, the pooling analysis of 3 European studies on decompressive craniectomy (DC) in patients with progressive middle cerebral artery infarction showed a reduction in mortality and an improvement in functional outcomes.1 That study and a subsequent study on elderly patients produced class I evidence in favor of this treatment.2 More recently, the investigators of the Rescue intracranial pressure trial with DC as last-tier therapy concluded that DC in patients with severe traumatic brain injury (TBI) and refractory intracranial hypertension resulted in lower mortality and higher morbidity at 6 months, whereas at 12 months a higher rate of favorable outcomes was statistically significant in the surgical group.3 Despite the mixed evidence regarding the effect of DC on functional outcome after the procedure, the use of this surgical strategy is on the rise, with 199 articles published in peerreviewed journals in 2017 (www.ncbi.nlm.nih.gov/pubmed) as compared with only 53 articles in 2007. This trend can be explained by the perception that in most cases it may represents a life-saving procedure where all other therapeutic measures have failed. After the acute stage of the primary disease, cranioplasty (CP) plays a key role in restoring the normal function and anatomy of the cranial vault. Considering that CP is not exempt from risks, identification of the safest reconstruction technique is crucial to achieve better functional recovery. Heterologous prostheses are able to overcome a series of problems related to the storing and conservation of autografts and to avoid bone resorption4-6; nevertheless, any proposed heterologous material has been demonstrated to be related to a specific spectrum of risks. The most recorded are bone reabsorption, infections, dislocations, and fractures.7 Porous hydroxyapatite (PHA) has received growing attention during the past decade. The high potential of stability and osseointegration has improved its use as a common material for biologic implants, including CP. Most clinical experience of CP with PHA refers to retrospective analyses and single-center studies. In this article, we report a multicenter prospective follow-up analysis of 149 patients who have undergone CP with PHA prostheses. In particular, we focus on the incidence of adverse events and implant removal.

Patients and methods

From January 2001 to December 2015, we conducted a prospective multicenter study on a case series of 149 adult and pediatric patients who underwent CP with custom-made PHA flaps after DC for several reasons. Custom-made CP flaps were designed with a standard reverse-engineering approach: from a fine-cut computed tomographic scan (less than 6 weeks between computed tomography and intervention), the producing company (Fin-

ceramica Faenza SpA, Italy) created a 3-dimensional model, which was first approved by the reference surgical team and eventually shipped in 2 copies (main prosthesis and backup copy) to the neurosurgical center. The primary endpoint was to define the incidence of adverse events after CP, with a particular focus on infections, implant fracture, and graft dislocation. Complications were further classified as minor and major depending on the need for surgical revision. The secondary endpoint was to define the incidence of adverse events requiring implant removal. Exclusion criteria were as follows: collagenopathies, immunodeficiency, movement disorders with postural instability, recent history of local or systemic infections, and use of intravenous drugs. Given that this was a purely observational study of a currently accepted surgical practice, ethical approval was waived. A thorough review of pertinent English literature was performed on Medline to explore the role of each type of CP and its specific impact on complications and global outcome.

Results

Over a period of 15 years (January 1, 2001, to December 31, 2015), 149 consecutive patients who had undergone CP intervention with custom-made PHA prosthesis were included in this study: 46 women and 103 men, with a mean age of 37.4 years (range, 6e74 years; median, 65 years). Table 1 shows the patients' features and demographics and also compares the Italian and French Centers; no statistically significant differences between the 2 countries were observed.

Primary Pathologic Features

The reasons for DC were duly recorded and can be summarized as follows: 1) 91 patients with severe TBI (61.1%), with a median age of 29.5 years and a male preponderance (84, 78%); 2) 38 patients with stroke (malignant middle cerebral artery ischemic strokes and intracranial hemorrhage) (25.5%), with a median age of 37.4 years; 3) 10 patients with primary or secondary osseous tumors (6.7%), with a median age of 51.5 years and a female preponderance (10 .7%); 4) 1 patient with brain tumor (0.7%); 9 patients with other causes (6.0%).

Location of DC and Time Interval with CP

The most common location of DC was the typical frontotemporoparietal flap (115 patients, 77.18%); whereas other less common locations (32 patients, 21.48%) included: frontoparietal, orbitofrontoparietal, orbitofrontoparietotemporal, temporoparietal, frontal, frontotemporal flaps. Standard bifrontal DC accounted for only 2 patients (1.34%). The side of DC was left in 66 cases (44.3%), right in 81 cases (54.36%), bilateral in 2 cases (1.34%).

Clinical and Radiologic Follow-Up

The time interval between DC and CP was between 2 and 6 months in 66 cases (44.3%), between 7 and 12 months in 43 cases (28.9%), and over 12 months in the other 40 cases (26.8%). The average time interval between CP and onset of complications was 33 months. All patients were evaluated at an initial time point of 30 days after the CP and thereafter were followed up at 6 months, 12 months, between 15 and 24 months, and finally at 3, 4, and 5 years. The data available at those time points reflect 93.96%, 87.25%, 77.85%; 61.07%; 47.65%, and 36.24% of the case series, respectively. Among the 149 patients included, 25 complications (16.8%) were recorded (Table 2).

Complications

Table 2 shows the 25 patients with complications (16.7%); 9 patients (6% of the whole case series) required removal of the prosthesis, of whom 7 had infections, 1 had fracture of the implant, and 1 had dislocation of the implant. Whereas no demographic factor could predict complications in general (Table 2) (univariate P nonsignificant for all recorded data), the removal of the CP was related (c2 and Fisher tests, $P < 0.01$) to a previous infection. Of 7 patients with late infections that required explantation of prostheses, 5 were second-line patients as compared with 22 of 149 (14%) in the general population.

Clinical Outcomes

The Glasgow Outcome Score extended evaluated at least 6 months after implantation in all suitable patients and showed a median score of 5 (standard deviation 3), mean 6.8 (range, 3e8). In the 9 patients in whom the CP was removed because of complications, 6 received the backup hydroxyapatite (HA) CP after at least 6 months from explantation in the same institution, whereas 3 patients were lost to follow up.

Discussion

The epidemiologic data of this study show some differences between the 2 countries. Even if not statistically significant, the causes of decompression were slightly different, with more TBI in Italy and more ischemic infarction in France. In addition, the bone flaps used were almost only unilateral, which means that, at least in trauma, the cause of decompression was a primary decompression possibly related to hematoma evacuation.8 Only 2 patients had a bifrontal reconstruction, which is used in the case of secondary decompression driven by intracranial pressure monitoring.3 There is considerable controversy concerning the timing of reconstruction. Whereas most of the articles are in favor of early reconstruction (2e3 months after decompression), others favor a delayed approach.9,10 Our series show in both countries a similar approach, with most patients being treated within 12 months and a significant number (44%) within 6 months. It has to be noted that this is a series of cases

starting in 2001, and the attitude of neurosurgeons in Europe toward earlier reconstruction has increased in more recent years. In our clinical practice, we have witnessed an increase in CP surgery over the past decade, mostly resulting from a higher rate of primary and secondary DC. Meanwhile, there has been no consensus about the best technique and material to be used for custom-made flaps.7 Similarly, the complication rates related to synthetic prosthesis reported in the literature are quite variable and can be estimated between 0% and 36%.11-21 This variability may be partially explained by the heterogeneity of the biomechanical characteristics of the implanted materials. The only report of a complication rate of 0% is a recently published article about a prospective series of patients treated with titanium CP.11 This report was published by the same group that in 2013 reported a complication rate with titanium of 29% in 14 years.14 The only difference seems to be that in the last series, all operations were performed by the senior surgeon, with more attention to preserve sterility. It seems difficult to believe that this is enough to obtain a zero complication rate with a metallic material, which is not bone integrated. CP provides several advantages in terms of neurophysiologic recovery, in particular for cerebral blood flow, cerebrospinal fluid circulation, intracranial venous pressure, and brain metabolism. 22-25 Nevertheless, additional evidence is still needed concerning proper CP timing, as we mentioned above, and, in cases of heterologous implant, the best material to use.26,27 Ideally, CP should be able to guarantee good esthetic results and early availability, and the implant should be made of a biocompatible, light, durable, and radiolucent material, resistant to infections and traumas. PHA seems a good candidate for CP because HA itself is the main constituent of bone (60%), and custom-made PHA has been shown to hold excellent biocompatibility because of the absence of host immune reactions and systemic/local toxicity.28,29 The prostheses used in our study are dense and have a high porosity (40% to 70% of total volume). The first article reporting a series of 25 cases of HA patients was published in 2007,30 but only until 2013 was a retrospective study of the epidemiologic and pathologic data in a significant number of cases published,31 These cases were extracted from 1608 postmarket safety information charts obtained by the company producing custom-made PHA CP (Custom Bone Service Fin-Ceramica, Faenza; period covered 1997e2010). Similarly to our experience, the authors of that study reported that PHA was used in 53.8% of patients for DC after TBI or intracranial hemorrhage, whereas in the remaining patients, HA was used for treatment of comminuted fracture, cutaneous or osseous resection, cranial malformation, autologous bone reabsorption, or infection or rejection of previously implanted material. The authors focused on adverse events specifically related to the custom-made flap and did not provide a comprehensive report of all postsurgical complications. These data demonstrated a lower incidence of adverse events

in patients treated with CP as firstline treatment, compared with a second-line option, as it was for our patients. Adverse events included early (before discharge) and late posttraumatic fracture of the CP, mobilization of the custom-made flap, and infections of the CP; noteworthy, the incidence of infections was higher in patients with a history of TBI and bifrontal DC. Two recently published prospective studies compared the HA prosthesis with other materials. Iaccarino et al.32 demonstrated that in 50 patients with HA prostheses, 1 case of infection (2%) and 1 case of fracture (2%) occurred, both requiring removal of the device. Lindner et al.33 compared HA and titanium implants and demonstrated an infection rate of 7.7% in HA patients as compared with 35.7% in titanium patients—data in complete contradiction with the recent finding of Honeybul et al.11 The infection rate of HA patients is similar to that in our study (6.7%), and there was no mention of HA fractures in the HA group, whereas there was a higher number of postimplantation epidural hematomas, 3 of which required explantation. Reviewing the literature on synthetic CP, subsidence, mobilization, and fractures have been demonstrated to present a higher incidence of subsidence, mobilization and fractures compared with autologous grafts. Conversely, autologous grafts tend to be susceptible to resorption and osteomyelitis. Several surgical series of other synthetic CP implants have been published in recent years. Honeybul et al.11 found a 16% bone resorption rate among 32 patients with autologous CP. Kim et al.12 compared both bone resorption and infection rate in 2 groups of patients undergoing CP using polymethyl methacrylate versus autologous graft. They found no difference in the infection rate (8.2% vs. 6.7%); conversely, they reported a remarkable difference in terms of bone resorption (0% vs. 60%, respectively). Finally, Thien et al.13 reported a series of CP with polyetherketone in which the overall complication rate was 25% and the implant failure was 12.5%. The above differences may reflect the different characteristics of the implanted materials: bioinertia (such as in titanium, which offers direct contact with bone tissue), biotolerance (such as in polyether ether ketone or polymethyl methacrylate, which create fibrous tissue at the interface with bone), and bioactivity (such as in autologous graft or PHA, which induces osseointegration by chemical bonding of bone tissue with the implant). In 2015, Fricia et al.34 demonstrated bony cell colonization of the graft in a 2- year histologic analysis of PHA CP with newly formed bone remarking PHA bony-induction capacity. In our series, we had an infection rate of 6.7%, of which 4.8% of patients required surgical revision. Zanaty et al.,35 in a series of 348 patients in whom the vast majority (67%) were treated with autologous bone, reported an infection rate of 26.4%, of which 56.5% were superficial and 43.5% were deep infections, and 31.5% of patients had both a superficial and a deep infection. In our series, only 3 of 149 (2%) patients reported hemorrhagic complications. Of those, only 2 (1.4%) required hematoma evacuation. Zanaty et al.35

published a rate of revision surgery for hematoma evacuation after CP of 6.89%. The rate of new-onset seizure after CP was 3.4% (5/149 patients) in our series, versus 14.44% according to Zanaty et al.35 One point deserving attention is the risk of fracture in patients with PHA CP. This topic has been discussed repeatedly in scientific meetings and, according to the production company, can be estimated at about 1% to 2% of cases. In our series, we found only 2 cases of fracture in 149 patients (1.4%) operated on with this custom-made flap; implant revision was deemed appropriate in only 1 case (0.7%). This is in agreement with the findings of previous prospective studies by Iaccarino et al.32 and Lindner et al.33 By contrast, Moles et al.36 recently reported that 10 of 44 patients in their series experienced fracture of the PHA flaps: 1 fracture was due to intraoperative drilling of the prosthesis (not recommended by the productionycompany), 6 fractures were incidentally found on postoperative computed tomographic scans, and 3 fractures were caused by mechanical second traumas (falls and road traffic accidents). Only the 3 patients with posttraumatic fractures required intervention, whereas the others were treated conservatively, with 1 case of spontaneous healing on radiologic follow-up. This study confirms that HA CP is fragile to second traumas in the first year of implantation before bony integration occurs. By contrast, "fractures" found incidentally at follow-up can disappear with no clinical significance. This study also confirmed that up to 49% of the custom-made PHA flaps show radiologic signs of bony integration within 2 years after the surgical procedure.33 Radiologic features, such as density expressed in terms of Hounsfield units in a region of interest, may underestimate bony integration, which would be better studied with nuclear medicine investigation capable of demonstrating in vivo the osteoblastic activity and vascular ingrowth (planar scintigraphy with radiophosponates such as Tc-99m methylene diphosphonate). 37 The results with this technique have been more in line with histologic and electron microscopic findings in experimental models that have demonstrated new bone formation inside the graft within 6 months from implantation and newly formed bone increase by over 300% between 6 and 12 months.38 Finally, our study allowed the assessment of correlations between the use of CP with PHA at any given point and the final outcome in terms of GOS-E. Based on our data we can certainly confirm a positive effect of CP on the overall wellbeing of our patients. This was confirmed also by Moles et al.,36 who reported significantly higher patients satisfaction with the cosmetic results offered by PHA versus those treated with autologous grafts (92.5% vs. 74.3%) and specifically by Lindner et al.,33 who demonstrated a higher rate of good recovery in HA patients than in to titanium patients.

Conclusions

The use of HA for cranial implants appears at least as safe as other heterologous materials with a biologic potential of osseointegration. The risk of explants seems to be significantly higher in second-line patients—data that were not shown in previous studies.32

Limitations of the Study

The length of the trial allowed the accumulation of a broad amount of data with a long follow-up times, even though some patients were lost during this period. Of note, despite the large case series and multicenter design, the present prospective trial had no control arm to compare the results of PHA CP with autografts or other synthetic CP. In addition, the study was not designed to specifically compare outcomes between early and late CP. Further prospective studies are advisable in the future.

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Tables

Table 1. Demographics of Patients According to Countries

	Country					
	France		Italy		Total Case Series	
	Number	%	Number	%	Number	%
Sex	1	2.0	.	0.0	1	0.7
F	16	32.0	29	29.3	45	30.2
M	33	66.0	70	70.7	103	69.1
Total	50	100.0	99	100.0	149	100.0
Age						
<24 years	9	18.0	34	34.3	43	28.8
25–34 years	8	16.0	21	21.2	29	19.4
35–44 years	11	22.0	13	13.1	24	16.1
45–54 years	10	20.0	17	17.2	27	18.4
55–64 years	11	22.0	10	10.1	21	14.0
65–74 years	1	2.0	4	4.0	5	3.3
≥75 years	.	0.0	.	0.0	.	0.0
Total	50	100.0	99	100.0	149	100.0
I–II line treatment						
I Line	44	88.0	83	83.8	127	85.2
II Line	6	12.0	16	16.2	22	14.8
Total	50	100.0	99	100.0	149	100.0
Follow-up length (months)						
<12 months	15	30.0	4	4.1	19	12.8
12 months	8	16.0	6	6.1	14	9.4
24 months	9	18.0	16	16.1	25	16.7
36 months	7	14.0	13	13.1	20	13.4
48 months	4	8.0	14	14.1	18	12.1
60 months	7	14.0	46	46.5	53	35.6
Total	50	100.0	99	100.0	149	100.0
Initial pathology						
Cerebral tumor	1	2.0	.	0.0	1	0.7
MCA ischemic stroke	11	22.0	1	1.0	12	8.1
Osseous tumor	2	4.0	8	8.1	10	6.7
Other	8	16.0	1	1.0	9	6.0
Trauma	20	40.0	71	71.7	91	61.1
Vascular	8	16.0	18	18.2	26	17.4
Total	50	100.0	99	100.0	149	100.0

MCA, middle cerebral artery.

Table 1. Demographics of Patients According to Countries

Table 2. Complications and Implant Removal

	Complications	Implant Removal	
Complication	**Number (%)**	**Number (%)**	**% Implant Removal**
Dislocation	1 (4%)	1 (11.1%)	100.0
Epilepsy + hydrocephalus	1 (4%)	.	0.0
Epilepsy	4 (16%)	.	0.0
Extradural hematoma	1 (4%)	.	0.0
Fracture	3 (12%)	1 (11.1%)	33.3
Hydrocephalus	1 (4%)	.	0.0
Infection	10 (40%)	7 (77.7%)	70.0
Cerebrospinal fluid leak	1 (4%)	.	0.0
Mobilization	1 (4%)	.	0.0
Subdural hematoma	1 (4%)	.	0.0
Cerebral hemorrhage	1(4%)	.	0.0
Total	25	9	36.0

Table 2. Complications and Implant Removal

5.2 Comparison between the different types of heterologous materials used in cranioplasty: a systematic review of the literature

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Originale article
J Neurosurg Sci. 2019 Dec;63(6):723-736.

Abstract

INTRODUCTION: The choice of heterologous materials for cranioplasty after decompressive craniectomy is still difficult. The aim of this study is to examine the association between material of choice and related complications to suggest the best treatment option.
EVIDENCE ACQUISITION: A systematic review was performed for articles reporting cranioplasty comparing the following heterologous implants: titanium, poli-methyl-methacrylate (PMMA), polyetheretherketone (PEEK) and hydroxyapatite (HA). Extracted data included implant materials and incidence of the most frequent complications.
EVIDENCE SYNTHESIS: The final selection resulted in 106 papers but according to our rules only 27 studies were included in the final analysis. Among a total of 1688 custom-made prosthesis implanted, 649 were titanium (38.49%), 298 PMMA (17.56%), 233 PEEK (13.82%), and 508 were HA (30.13%). A total of 348 complications were recorded out of 1688 reported patients (20.64%). In the titanium group, 139 complications were recorded (21.42%); in the PMMA group 57 (19.26%), in the PEEK group 49 (21.03%) and in the HA group 103 (20.3%). If we examine a summary of the reported complications clearly related to cranioplasty (postoperative infections, fractures and prosthesis displacement) versus type of material in multicentric and prospective studies we can see how HA group patients have less reported infections and cranioplasty explantation after infections than PMMA, PEEK

and titanium. On the contrary HA patients seem to have a higher number of prosthesis displacement again if compared with the other materials. Since these data are not derived from a statistically correct analysis they should be used only to help to differentiate the properties of the various heterologous cranioplasties.
CONCLUSIONS: The ideal material for all heterologous cranioplasty has not yet been identified. The choice of material should be based on the clinical data of patients, such as the craniectomy size, presence of seizures, possibility of recovery, good long-term outcome associated with a cost analysis.

Introduction

Cranioplasty is a critical stage of cranial defect reconstruction while the history of cranioplasty encompasses hundreds of years.[1] Recently, there has been a tremendous increase in the number of peer-reviewed papers published on cranioplasty (from 25 in 2000 to 168 in 2017, about seven times more).[2] This increase is only partially due to the resurge of the technique of decompression, where in the same period papers describing decompression technique increased from 94 to 199, as can be seen searching Pubmed.[3] When available, autologous bone is still considered the treatment of choice, but due to several restrictive storage regulations and the high rate of resorption,[4, 5] its use as first choice for cranial reconstruction is now under discussion in the Western world. In recent years, different alloplastic materials have become available for cranial reconstruction.
Patient-specific and surgery-specific factors have been reported to be the most important determinant of complication rates following heterologous cranioplasty.[6] Furthermore, the type of alloplastic material seems to influence the complication rates. The "ideal" material should match the biochemical and biomechanical properties of the replaced tissue, fitting the cranial defect and achieving a complete closure, while being easy to sterilize, resistant to heat and mechanical breakdown, biocompatible, chemically inert and non-exothermic. Finally, it should not interfere with the imaging techniques (CT or MRI). The choice of material also depends on patient pathology, age, size and location of the cranial defect.[7, 8]
Over the years, several types of materials have been developed in order to satisfy most of these criteria. The most common alloplastic materials used for cranioplasty are: metal substitutes (titanium), acrylics such as poli-methyl-methacrylate (PMMA), plastics such as Polyetheretherketone (PEEK) or different types of bone cement or bioceramics such as Hydroxyapatite (HA). A direct comparison with similar products is not easy and very few papers have offered prospective studies comparing different heterologous materials[9, 10] and/or different materials versus autologous bone.[11-13] Whereas in decompressive craniectomies two large prospective multicentric studies have been published,[14, 15] nothing similar has occurred in cranial reconstruction. There are only few prospective multicentric

studies, most of which limited only to one Country. The purpose of this study is to compare the number of complications and implant removal of titanium, PMMA, PEEK and HA. Furthermore, for the first time our aim was, based on a correct evaluation of published papers, to offer a practical suggestion (if at all possible) regarding the best heterologous material for the various types of cranial reconstruction.

Evidence acquisition

Search strategy

A systematic review of the literature was performed for published articles reporting on complications of cranioplasty after craniectomy. PubMed/ MEDLINE, Scopus, and the Cochrane Database of Systematic Reviews were used to search the following keywords: "cranioplasty," "cranioplasty complications," "decompressive craniectomy," "decompressive craniectomy complications" ''cranioplasty, hydroxyapatite," ''cranioplasty, custom bone," "cranioplasty, custom bone, cranial defects reconstruction," "hydroxyapatite, 3D design technique," "cranioplasty acrylic materials," "cranioplasty titanium," "cranioplasty PMMA," "cranioplasty PEEK" and ''cranioplasty, hydroxyapatite." The selected keywords were included in the title, abstract, or keywords list. The search was restricted to original clinical studies published between January 1987 and January 2018.

Study selection

In this study, we included articles reporting complications in human patients following heterologous cranioplasty. We considered only articles describing the use of techniques involving threedimensional (3D) modelling and reconstruction, and computer-aided design/computer-aided manufacturing (CAD/CAM) or describing intraoperative prosthesis and plate reconstruction on previously acquired 3D models. After a first screening, case series, editorials, Case–control studies, cohort studies, retrospective studies, systematic reviews, meta-analyses or clinical trials considering the complication rates of any type of cranioplasty were included. Meta-analyses and systematic reviews were thoroughly screened for possible inclusion. Any non-English article was excluded. Studies that involved animals were excluded. Case reports, and technical notes and editorials were excluded. Studies that included patients with non-decompressive craniectomy (for example, the resection of skull tumors followed by cranial reconstruction) were collected.

The exclusion criteria were:

- case series with less than 10 patients;
- all studies with a paediatric population; authors decided to consider as pediatric any patient aged under 14 years of age and any patients indicated as pediatric in the

studies selected;

• non custom-made cranioplasties.

The results were independently screened by tree of the authors (C.M., C.I and I.Z.); disagreements were solved by consensus among all the Authors.

Data extraction

The following data were extracted from each article, if clearly reported: year of publication, Journal of publication, type of study, level of evidence (using the Elsevier level of evidence chart), number of neurosurgical centers involved (single or multicentric study), number of patients, epidemiological data (gender, average age) indication for craniectomy, material used for cranioplasty, types of complications, average follow-up and surgical times. Complications were grouped into the following categories: total overall complications; infections; rejections; hematomas, which includes all types (epidural, subdural and intracranial); fluid collections, mechanical complications which includes all cases of non-union, mobilization and fractures; hydrocephalus.

Evidence synthesis

The papers search was carried out on PubMed, SCOPUS and Cochrane Library: no studies regarding the topic of study were found in Cochrane library; instead, the research on PubMed and on SCOPUS was complementary.

The selected keywords were used to search PubMed database: “cranioplasty” (1628 items found), “cranioplasty complications” (787), “decompressive craniectomy” (1990), “decompressive craniectomy complications” (951), ‘‘cranioplasty, hydroxyapatite” (117), “cranioplasty, custom bone” (105), “cranioplasty, custom bone, cranial defects reconstruction” (39), “cranioplasty, 3D design technique” (11), “cranioplasty acrylic materials” (29), “cranioplasty titanium” (229), “cranioplasty PMMA” (89) and “cranioplasty PEEK” (48). The selected keywords were included in the title, abstract, or keywords list. The search was restricted to original clinical studies published between January 1987 and January 2018. Therefore 6023 records were identified through the database. Literature review results were included in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1). In the second step of screening, 5751 studies were excluded because the Full-text articles were not available, or assessed for eligibility according to the following exclusion criteria: laboratory study, animal study, inconsistent title, articles not in English. From the remaining 272 studies, 166 articles were removed according to the following exclusion criteria: meta-analysis, systematic reviews, not enough patients (<10 cases), text in non-English language. The research resulted in 106 peer-reviewed publications. These papers were considered for further analysis and inserted in our database. These studies were then divided according to the “Levels of Evidence for

Primary Research Question," which comprises 5 levels based on the levels of quality[16] 1 study was LeveI I (0.94%), 14 studies were Level II (13.21%), 90 studies were classified as Level III (84.91%), 1 study was Level IV (0.94%) and 0 studies were Level V. In the 106 papers, the indications for cranioplasty included 12269 decompressive craniectomies (DC) with unspecified causes (29.52% of patients), 5126 trauma (12.33% of patients), 2718 vascular diseases (6.54%), 3169 erosive tumors (7.63%), 1549 congenital malformations (3.73%), 697 infections (1.68%) and 1884 other causes (4.53%), such as revision surgery (4.55%) or other indications. Several studies included only trauma patients and many of them did not specify the reason for the surgery (14,146 patients, 34.04%). The mean follow-up, when indicated, was 27 months. With the aim of identifying a possible correlation between the different heterologous materials used

for cranioplasty and the postoperative complication encountered, we performed a comparative analysis of the reported complications, selecting retrospective and prospective studies which considered postoperative complications in custom-made reconstruction in titanium, PMMA, PEEK and HA. These heterologous materials are, by far, the most used in cranial reconstruction. New materials have been recently introduced[17] but as in the case of fiber-glass reinforced composite[18] or electronic beam technology and titanium powder[19] the number of published cases is too small for a meaningful comparison with the other materials. Therefore, at the conclusive screening of the previously analyzed 106 articles, we have only considered 27 articles. The exclusions criteria were: studies including a pediatric population (as defined above) (=11), systematic reviews and Meta-analysis (=20), editorials (=6), technical notes (=8), case series and case reports (=29), laboratory studies with animals (=5). Out of the 27 selected papers, two papers describe randomized clinical studies,[10, 11] therefore presenting a high level of evidence and a limited risk of bias. The remaining 25 articles have been classified according to Newcastle-Ottawa grading scale (NOS scale).[20] The scale has a maximum rating of 9 (absence of bias) and a minimum of 1. Six were prospective studies, 20 were retrospective studies, 8 were comparative studies (3 prospective, 4 retrospective) and 8 were multicenter studies. Only 12 of the 25 studies earned more 5 stars, and the highest score was 7 stars. Therefore according to the scale most of the selected studies had a high risk of bias.

Complications

In the 27 selected studies, a total of 1686 custom-made prostheses were implanted: 649 were in titanium (38.49%), 298 in PMMA (17.56%), 233 in PEEK (13.82%), and 508 were in HA (30.13%). Different to other materials, a large number of patients with a HA implant (4246 patients in 2 different studies) were reported following company postmarketing studies and not single or multicentric publications.[21, 22] To allow comparison between the different

materials with similar studies, these patients were not inserted in the tables of the study but were considered only for discussion. For each study we calculated the overall number of complications imputable to surgical procedures and for each reported complication we calculated the average value. Additionally, we reported the overall surgical revision rate after complications, and the surgical revision rate for each complication.

We recorded the following postoperative complications: postoperative epidural hematoma (EH), postoperative fluid collection (FC), postoperative infection (IF) (superficial and deep infections), prosthesis fracture (FR), prosthesis displacement (PD) and postoperative hydrocephalus (H). A total of 348 complications were recorded out of 1688 reported patients (Table I, II, III, IV).[7, 10, 11, 23-36, 38-45]

The overall complication rate of all the heterologous materials considered was 20.64%.

In the titanium group, 139 complications were recorded (21.42%); in the PMMA group 57 (19.26%), in the PEEK group 49 (21.03%) and in the HA group 103 (20.3%). Two hundred and ten cases of surgical revision were registered (12.45%). 78 cases in the titanium group (12.01%), 52 in PMMA group (17.57%), 31 in PEEK group (13.3%) and 49 (9.7%) in HA group.

Epidural postoperative hematomas

Fifty-seven cases (3.38%) of postoperative epidural hematomas were recorded. Thirty in the titanium group (4.62%), 2 in the PMMA group (0.68%), 11 in the PEEK group (4.72%), and 14 in the HA group (2.8%).

Out of the total cases of EH, 32 patients need a revision surgery due to postoperative hematoma evacuation (56.14%). 18 patients (2.77%) in the titanium group, 2 patients (0.68%) in the PMMA group, 6 patients in PEEK group (2.58%), and 6 patients in HA group (1.2%).

Fluid collections

Sixty-one patients (3.62%) reported postoperative fluid collection and 12 of them required surgical revision (19.67%). 38 (5.86%) fluid collections were recorded in the titanium group and 7 of them (1.08%) required revision surgery. One (0.34%) fluid collection was observed in the PMMA group with 1 (0.34%) surgical revision, 11 (4.72%) fluid collections were recorded in the PEEK group, 4 (1.71%) of them required revision surgery and 11 (2.17%) fluid collections were observed in the HA group, with no revisions performed (0%).

Infections In this study we considered all types of infections: superficial infections, deep infections, infections requiring surgical solutions and infections treated with an antibiotic solution. Among the superficial infections, we considered wound infections, necrosis, surgical site infections and subgaleal infections. Among the deep infections, we considered abscess formation, epidural subdural empyema or meningitis and ventriculitis and prosthesis infections requiring surgical treatment. Postoperative infections were recorded in 151 patients (8.96%): 66 (10.17%) infections were recorded in the titanium group, 31

infections (10.47%) in the PMMA group, 17 (7.29%) in the PEEK group and 37 (7.3%) in the HA group. One hundred and twenty-four patients (7.35%)
required a second surgery for postoperative infections: 50 cases in the titanium group (7.7%), 30 in the PMMA group (10.14%), 14 in the PEEK group (6.01%), and 30 in the HA group (5.9%).

Mechanical complications

As mechanical complications we considered graft fracture or displacement.

Fracture of the prosthesis occurred in 21 implanted prosthesis (1.35%): 2 fractures occurred in the titanium group (0.31%), 1 fracture in the PMMA group (0.34%), in PEEK group 0 fractures were recorded and 18 fractures (3.5%) were observed in HA group. A total of 7 revision surgeries (0.45%) were performed for prosthesis fractures. In 5 cases of HA fracture (0.98%), in 1 case of titanium (0.16%) fracture and in 1 case of PMMA fracture (0.34%).

Prosthesis displacement occurred in 34 cases (2.02%) and 16 underwent revision surgery (0.95%). All types of displacements were considered. Two case (0.31%) was recorded in the titanium 1 (0.15%) of them required surgical revision; all 11 patients (3.72%) in the PMMA group required revision surgery, 3 patients (1.29%) of the PEEK group with prosthesis mobilization did not require surgical revision and 4 (0.8%) of the 18 (3.54%) displaced HA prosthesis required a second surgery.

Hydrocephalus

According to literature we have included postoperative hydrocephalus among cranioplasty complications. A total of 24 cases (1.42%) of hydrocephalus were recorded and 19 of them (1.13%) required surgical treatment. One case (0.15%) was found in the titanium group, which was surgically revised; 11 cases (3.72%) in the PMMA group and 7 cases (2.36%) of them were revised. Seven cases (3.01%) were recorded in the PEEK group and all of them required surgical revision. Five cases (0.9%) were recorded in HA group and 4 (0.79%) of them underwent revision.

Separate analysis of prospective studies

In Table I, II, III, IV we have marked the prospective published papers, divided by material used and the number of centres involved (monocentric vs. multicentric). Multicentric studies were considered separately since it is known that monocentric studies may contain biases.[46] In prospective monocentric analysis it is possible to notice the absence of study for titanium and PEEK; similarly, there are no studies in the multicentric papers on PMMA and PEEK; HA was the only material analyzed in all prospective studies.

Summary of relevant data We have summarized in the following tables the reported complicated cases in order to compare the various heterologous materials. We deliberately

did not perform any statistical analysis since the methods of data collection, the length of follow up and the reported complications were extremely different in the selected publications. Only complications clearly related to the cranioplasty (postoperative infections, fractures and displacement of the prosthesis) were included in these tables. More, we reported only the most significant findings in terms of comparison among the various materials. Other complications like postoperative hematomas, postoperative fluid collections and hydrocephalus which can be related to other factors like type of decompression, brain compliance and previous ventricular dilatation were not included but are present in Table I, II, III, IV.

In a pooling analysis of all studies (retrospective, prospective, mono and multicentric) no significant comparative data were reported. We therefore only examined multicentric and prospective studies. In Table V we report all cases included in multicentric studies. In this case only titanium, PEEK and HA are reported. The clinically most interesting data are less postoperative infections also requiring a second operation in HA group compared to PEEK and titanium groups. The opposite is seen for prosthesis displacement with less displacements in titanium and PEEK groups. In Table VI we report all prospective studies. Only titanium, HA and PMMA (with much less patients) are included. PMMA and HA patients had less postoperative infections and less surgical revision for infections than titanium patients. HA patients had more fractures (but most of them did not require a surgical revision) and more displacements in the postoperative period compared to titanium and PMMA. In Table VII we report prospective multicentric studies which should be the most reliable clinical studies. Only titanium and HA are included: The number of infections requiring a second surgery was less in HA group whereas the number of cranioplasty displacement was higher in HA and lower in titanium group.

Discussion

The first consideration is that, in spite of a tremendous increase of interest in the procedure of cranial reconstructions, there are only eight prospective clinical studies and only five published papers if we take into account the multicentric prospective studies.

There is a clear limit to multinational studies since the distribution of materials is different in the various Countries: titanium is mostly used in Australia, UK and Germany[10-12, 36] PMMA in the USA[23, 25] PEEK in the USA, Singapore and Korea[26, 31-33] HA in France and Italy.[41] The result is that the multicentric studies are either mono-national[9, 10] or bi-national only in the case of the similar use of materials, as in France and Italy.[41] A large national database may help in collecting sufficient data to study the complications related to the various cranioplasty materials. Unfortunately, the UK database[47] and the German

database[48] still have not produced any paper, while data from the Finnish database only concern the use of autologous bone[49] and the related risk of complications.

In the USA, a large national-based study with more than 8000 patients has just been published.[50] The target was the study of timing and size of cranioplasty as compared to outcomes. The only reference to the material was that allograft cranioplasty in the "emergency" group had a higher rate of complications as compared to non-allograft. There is no description of non-allograft cranioplasty. Recent reviews[5, 51] and prospective studies[9] show that autologous bone has a complication rate statistically higher than any heterologous material. This is almost entirely due to the specific complication of the autologous bone, which is reabsorption in about 20% of cases.[51] Since this phenomenon seems to be more frequent in post-traumatic cranioplasty, it has been proposed that autologous bone should no longer be the first choice in post-traumatic reconstruction. On the other hand, to our knowledge only few papers[8] dealt with all the available materials in order to support the choice of the "best" material to be used and no review has separated retrospective from prospective papers and multicentric from monocentric studies as we have done.

In our review, we have only taken into consideration 3D custom-made reconstructions since we believe that in the "Western" world, in 2018, this is the only way to restore the cranial vault. This is totally different from countries with limited resources where often even autologous reconstruction is difficult. To avoid cranial reconstruction, a proposal for keeping the bone on the site of craniectomies has been done using a technique called hinge craniectomy.[52] Before discussing the complication rate, we have to consider the role of cranial reconstruction that is not only cosmetic but also therapeutic.[53-55] A recent class I study on decompression[15] showed a marked improvement in patient outcome between six and twelve post-traumatic months. Until few years ago, during the time of data collection for the Rescue intracranial pressure (ICP) study, most cranial reconstructions were performed in Europe during this period.[41] The link between lifesaving surgery like cranial decompression and cranial reconstruction followed by intensive rehabilitation is very strong.[41] Unfortunately, the link between decompression complications[56] and reconstruction complications[4, 5, 57] is also important.

Complication rate

It is to be noted that our paper differs from recently published reviews[4, 5] since we have excluded papers with less than 10 patients reported and we have included only 3D printed custom-made cranioplasties, so our population concerns almost only papers published over the last 11 years and can only partially be compared with previous reports. We have also divided the studies into retrospective and prospective and then added the subcategory of multicentric study since it is known that studies performed in a single centre may present

biases.[46] The overall complication rate in our survey was about 20% in a pooling analysis of all the published studies and it was similar for the various materials. Unfortunately, the published data do not help us. The rate of complication can be as low as 0 in only one series[58] and as high as 36% in a recent American national survey.[50] All the possible rates in between have been published. Surgical revision rate for the whole group was 12% with a trend toward fewer surgical revisions in titanium and HA patients.

Our data matches well with the 11.6% of revision rate for synthetic material recently published by Malcom et al.[4] and it is higher than the 6.6% recently reported by van de Vijfeijken.[5]

Materials

Titanium

Among metal grafts, titanium is currently the only one used for repairing cranial defects. Titanium (Ti-6-4), also known as grade 5 surgical titanium (Ti 6AI-4V),[59] was introduced in 1965[60] as a valid alternative to autologous bone and is to date largely use in moderate to large sized craniectomy defects because of its strength and biocompatibility, light weight malleability, and with virtually no risk of allergic reactions.[58]

In large series of retrospective studies the absolute complication rates range from 26.4% to 58.3% and the plate removal rate ranges from 8.4% to 10.3%.[16, 37, 39, 61-63] The most common complication after titanium cranioplasty is represented by infection, with a rate from 4% to 15%.[16, 35-37, 39, 64-66] Moreover, the infection rate following titanium cranioplasty in patients who originally underwent the surgical removal of an infected bone flap following primary surgery is 20%.[37, 58, 67] In cases of large skull defect reconstructions, infections range from 19% for bifrontal cranioplasties to 32% for hemicranioplasties.[35] All published data are in contrast with the results of a randomized controlled trial of Honeybul et al.[58] where no primary or secondary infections were recorded and no patient needed cranioplasty revision after titanium cranioplasty. Since the same group also published a much higher rate in a previous paper[35] the explanation was that surgery in the last series was performed only by the most experienced surgeon with more attention to standardized procedure to avoid infection. Other groups have shown that the rate of infections does not change with different surgeons.[68] This model cannot be adopted practically in large Units where a rotation among surgeons (including young neurosurgeons), performing cranioplasty is unavoidable.[58]

In our review, we included 7 relevant original articles in the titanium group. 3 articles were multicentric prospective studies[10, 17, 58] and 4 were retrospective studies (3 monocentric and 1 multicentric).[36-39] In our analysis, titanium presented in all the studies together with HA a significantly lower rate of postoperative hydrocephalus and a lower rate of postoperative fluid collections in prospective studies but these data do not seem to be related only to the

cranioplasty. In spite of the last discussed paper,[58] the overall rate of postoperative infections even requiring explantation was higher than PMMA and HA in prospective studies and higher again than HA only in multicentric studies

PEEK

PEEK is an aromatic polymer with ether and ketone chains used in cranial reconstruction surgery since the 2000s.[57, 69-71] Among alloplastic materials, PEEK is considered a first-generation bone substitute for its mechanical and chemical proprieties of thermal conductivity, resistance to high temperatures, chemical, radiation, and biologic inertness.[69, 72] PEEK can be computer-designed to fit precisely to the cranial defect.[73] PEEK implants developed postoperative complications in 15.3% of cases (ranging from 0 to 25%).

The overall rate of postoperative complications requiring surgical intervention was 8.7% (ranging from 0 to 12.5%).[33, 57] The infection rate ranged between 0% and 22%.[30, 32-34, 57] Jonkergouw et al.[31] recorded a high overall complication rate of 28% due to infection (13%), postoperative haematoma (10%), cerebrospinal fluid leak (2.5%) and wound-related problems (2.5%). All postoperative infections required removal of the implant with a secondary high reoperation rate (13%).[31] In our review, we included 6 relevant original articles in the PEEK group. The included articles were only retrospective studies. 3 were monocentric[7, 32, 34] and 3 were multicentric studies.[30, 31, 33] In the absence of prospective studies of PEEK, the only difference was the presence of a higher number of patients with hydrocephalus after a PEEK cranioplasty. As already stated it is difficult to attribute the occurrence of hydrocephalus only to the cranioplasty and not to the type and complication of decompression itself.

PMMA

PMMA is a mouldable acrylic resin that offers strength and protection similar to native bone tissue. It is stable, chemically inert, unaffected by temperature, nonconductive, well-tolerated by tissue, and easily placed and modified, and PMMA is one of the most biocompatible alloplastic materials currently available.

Different to HA, due to the lack of porosity, PMMA implants cannot be infiltrated by new bone tissue; they interfere with osteoconduction and vascularization, and do not interact with the surrounding tissue. Compared to Hydroxyapatite and PEEK, this material has been used for a longer time in the treatment of craniectomies, as the first article about it was published in 1949.[74] In a recent metanalysis, a general complication rate of 14.1% was reported, while the reoperation rate was not shown.[75] A similar rate of surgical site infection was reported for synthetic material (7.1%) with a rate of reoperation of 11.6% of the total infection.[51] For the purpose of our study, we considered 8 articles, classified as follows: 1 prospective monocentric study,[23] and 7 retrospective monocentric studies.[7, 24-29] If we

consider all retrospective and prospective studies, PMMA showed a lower rate of postoperative epidural hematoma as compared to the other materials, not confirmed by the rate of surgical evacuation but again these data cannot be attributed only to the cranioplasty itself. In all prospective papers PMMA (but only 57 patients from a monocentric study were included) showed together with HA a lower rate of infection as compared to titanium.

HA

HA is a naturally occurring mineral form of calcium apatite. Up to 70% of human bone weight is a modified form of HA. Due to its characteristics, HA is increasingly used to make bone grafting material as well as dental prosthetics, and for HA cranioplasty which is based on macro and micro porous hydroxyapatite. The chemical composition, combined with elevated porosity, allows remodeling through a cell-mediated process involving osteoclast activity, similar to new bone formation, and acts as a synthetic osteoconductive/osteointegrative scaffold after implantation, favoring osteointegration[76, 77] This material can be considered new, since the first publication regarding HA was written in 2000, and the first clinical paper with at least one-year follow-up was published in 2007.[45] However, any form of cranioplasty remains a surgical procedure carrying a complication rate. In the large postmarketing study, there were 51 infections (1.7%), with a reoperation rate of 25.49%.[21, 22] Lindner et al.[10] reported a 6-month infection rate of 7.7%, all of them reoperated as compared to 35.7% in titanium implants in the same study. A recent Italian-French study showed a global complication rate of HA implants of 16.8% with only 7 patients out of 149 requiring removal of the prothesis for infection (4.7%).[41] In the study of Moles[42] it was 12.5%, with a 66% rate of reoperation. Implant fracture is a complication related almost only to HA and due to the intrinsic fragility of the material until osteointegration occurs.[77] This has been reported as a significant disadvantage of HA cranioplasty.[78] In recently published studies,[9, 10, 40, 41] postoperative fractures occurred from 0.7 to 2% of the cases.

Only in a series published by Moles,[42] 10 out of 44 patients presented post op fracture. Six of those fractures were incidental findings on CT control and only 3 required (6.8%) a new surgery. This study[42] confirms the value of multicentric studies since in the published multicentric studies on HA[9, 10, 41, 44] the occurrence of fractures requiring a surgical treatment in HA patients is much lower. There are also cases of spontaneous fracture healing, as in Staffa and Moles,[42, 45] confirming the osteointegrative properties of the HA. A recent Belgian[77] report of 17 cases of HA implants showed some form of osteointegration of the implant in 12 cases (70%) at CT follow up. For the purpose of our study, we considered 8 studies related to HA: 3 prospective multicentric,[9, 10, 41] 2 prospective monocentric,[40, 42] 2 retrospective monocentric[43, 45] and 1 retrospective multicentric study.[44]

In spite of recent history, HA is, together with titanium, the most studied material in prospective studies. In our review, HA is the material with the lowest rate of infection also requiring surgery in retrospective multicentre studies and in all prospective studies. The particular composition of HA allows the formation of new microvessels as demonstrated by a recent study using gadolinium MRI,[77] thus making it possible in some cases of infection to use antibiotic therapy without prosthesis removal.[13] Concerning postoperative fractures, even if it is the more fragile material, the rate of surgical treatment for fractures is not significantly different from that of other materials. However, there is a higher number of prosthesis displacement, compared to titanium, even if the absolute numbers are small. This can be related to specific characteristics of HA implants where the use of plate and screws is impossible due to the initial fragility of the implant. Only silk sutures can be used to keep the prosthesis in place until osteointegration possibly occurs in about 6 to 12 months.

Practical suggestions

We have not performed any statistical analysis therefore our suggestions are more on a side of an "expert opinion" than of a strong evidence-based analysis.

From our review and other good quality papers we could say that:

• titanium and PMMA (also PEEK but with no prospective studies) offer immediate protection but no biological integration with the surrounding bone. The rate of complication seems similar;

• HA group has shown the lowest postoperative infection rate as well as the lowest rate of plate removal after an infection. In any case, the same material has a higher rate of displacement when stressed; therefore, it should be used for patients with less risk of a second trauma (patients collaborating with no epileptic seizures);

• the cost is also an issue: in our country (Italy) at present a unilateral large reconstruction with 3D technique costs about 7000 to 8000 euros for HA, 6000-7000 euros for PEEK, around 5000 for PMMA. For full titanium, since it is not available, we report the UK data on costs around 3000 euros.

Conclusions

Other recent reviews have concluded: "future studies should consider randomizing material selection, stratifying patients by primary pathology and directly comparing synthetic material headto- head"[4] or "This systematic review of a substantial body of evidence offers insufficiently strong evidence to conduct a meta-analysis or support the use of any material over another for cranioplasty"[5].

Also in our review we have seen that there is a high risk of bias (see methodological scoring with the Newcastle Ottawa Scale[20] in most of the selected studies and no study reached the

best scoring. Therefore the quality of the published papers is not enough to support strong clinical conclusions. What we previously said regarding therapeutic cranioplasty needing an ideal material[33] is unfortunately still true but we have to start using the available different heterologous cranioplasty for different patients. The choice of material has to be based on the clinical data of our patients, like decompression size, patient age, presence of seizures, possibility of recovery, good long-term outcome associated with a cost analysis.

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Tables

Table I.—Overall complications reported in the studies selected for PMMA group.

	Worm (P)[23]	Rossetto (R)[24]	Jaberi (R)[25]	Wachter (R)[26]	Bobinski (R)[27]	De Bonis (R)[7]	Goh (R)[28]	Huang (R)[29]
	2016	2015	2013	2013	2013	2011	2010	2015
Total PMMA (N.)	58	29	78	15	19	46	31	22
% PMMA on total cases	100	64.44	100	11	38.8	21.1	100	100
Male	44	NA	52	NA	14	NA	27	10
Female	14	NA	18	NA	5	NA	4	10
Average age	40±14	NA	43 (19-68)	NA	45.3±15.8	NA	28 (6-78)	44.7
Follow-up		17	10	>12	54.3	>18	21	34.2
Centers	1	1	1	1	1	1	1	1
Total PMMA epidural hematomas (N.)	2	NA	0	0	0	NA	0	0
% PMMA epidural hematomas on total HA implants	3.4	NA	0	0	0	NA	0	0
Surgical revision for PMMA	2	NA	0	0	0	NA	0	0

epidural hematoma (N.)								
% of surgical revisions / PMMA epidural hematoma	100	NA	0	0	0	NA	0	0
% surgical revisions for epidurals / total PMMA	3.4	NA	0	0	0	NA	0	0
Total PMMA fluid collections (N.)	0	NA	0	0	0	NA	1	0
% PMMA fluid collections on total HA implants	0	NA	0	0	0	NA	3.23	0
Surgical revision for PMMA fluid collections (N.)	0	NA	0	0	0	NA	1	0
% of surgical revisions for PMMA fluid collections	0	NA	0	0	0	NAN	100	0
% surgical revisions for fluid collections / total PMMA	0	NA	0	0	0	NA	3.23	0
Total PMMA infections (N.)	3	9	9	3	2	2	3	0
% PMMA infections on total PMMA implants	5.17	31.03	11.54	20	10.52	4.4	9.68	0
Surgical revision for PMMA infections (N.)	2	9	9	3	2	2	3	0

% of surgical revisions for PMMA infections	100	100	100	100	100	100	100	0
% surgical revisions for infections / total PMMA	3.4	31.03	11.54	20	10.52	4.4	9.68	0
Total PMMA fractures (N.)	0	NA	0	0	NA	1	0	0
% PMMA fractures on total PMMA implants	0	NA	0	0	NA	2.17	0	0
Surgical revision for PMMA fractures (N.)	0	NA	0	0	NA	1	0	0
% of surgical revisions for PMMA fractures	0	NA	0	0	NA	100	0	0
% surgical revisions for fractures / total PMMA	0	NA	0	0	NA	2.17	0	0
Total PMMA prosthesis deplacement (N.)	0	NA	1	3	2	3	0	2
% PMMA prosthesis deplacement on PMMA implants	0	NA	1.28	20	10.52	6.52	0	9
Surgical revision for PMMA prosthesis deplacement (N.)	0	NA	1	3	2	3	0	2
% of surgical revisions for	0	NA	100	100	100	100	0	100

PMMA prosthesis deplacement								
% surgical revisions for deplacements / total PMMA	0	NA	1.28	20	10.52	6.52	0	9
Total PMMA hydrocephalus (N.)	5	NA	NA	NA	6	NA	NA	0
% PMMA hydrocephalus on total implants	8.62	NA	NA	NA	31.58	NA	NA	0
Surgical revision for PMMA hydrocephalus (N.)	1	NA	NA	NA	6	NA	NA	0
% of surgical revisions for PMMA hydrocephalus	20	NA	NA	NA	100	NA	NA	0
% surgical revisions for hydrocephalus / total PMMA	1.72	NA	NA	NA	31.58	NA	NA	0

Table II.—Overall complications reported in the studies selected for PEEK group.

	Zhang (R)[30]	Jonkergouw (R)[31]	Thien (R)[32]	Rosenthal (R)[33]	De Bonis (R)[7]	Rammos (R)[34]
	2018	2016	2015	2014	2011	2015
Total PEEK (N.)	75	40	24	66	17	11
% PEEK on total cases	40.5	100	18.18	100	7.8	100
Male	62	23	13	46	NA	5
Female	13	15	11	19	NA	6
Average age	33.27	43	35	35	NA	46

Follow-up	13.5	19.1	16.9	24	>18	6
Centers	7	2	1	3	1	1
Total PEEK epidural hematomas (N.)	3	4	1	3	NA	0
% PEEK epidural hematomas on total HA implants	4	10	4.2	4.55	NA	0
Surgical revision for PEEK epidural hematoma (N.)	0	3	1	2	NA	0
% of surgical revisions / PEEK epidural hematoma	0	75	100	66.67	NA	0
% surgical revisions for epidurals / total PEEK	0	7.5	4.2	3.03	NA	0
Total PEEK fluid collections (N.)	6	2	0	2	NA	1
% PEEK fluid collections on total implants	8	5	0	3.03	NA	9.1
Surgical revision for PEEK fluid collections (N.)	1	1	0	1	NA	1
% of surgical revisions for PEEK fluid collections	16.67	50	0	50	NA	100
% surgical revisions for fluid collections / total PEEK	1.33	2.5	0	1.52	NA	9.1
Total PEEK infections (N.)	2	6	2	5	2	0
% PEEK infections on total PEEK implants	2.66	15	8.4	7.57	11.76	0
Surgical revision for PEEK infections (N.)	1	6	2	5	NA	0

% of surgical revisions for PEEK infections	100	100	100	100	NA	0
% surgical revisions for infections / total PEEK	1.33	15	8.4	7.57	NA	0
Total PEEK fractures (N.)	NA	0	0	0	NA	0
% PEEK fractures on total PEEK implants	NA	0	0	0	NA	0
Surgical revision for PEEK fractures (N.)	NA	0	0	0	NA	0
% of surgical revisions for PEEK fractures	NA	0	0	0	NA	0
% surgical revisions for fractures / total PEEK	NA	0	0	0	NA	0
Total PEEK prosthesis deplacement (N.)	1	0	1	0	1	0
% PEEK prosthesis deplacement on PEEK implants	1.33	0	4.2	0	5.88	0
Surgical revision for PEEK prosthesis deplacement (N.)	1	0	0	0	NA	0
% of surgical revisions for PEEK prosthesis deplacement	100	0	0	0	NA	0
% surgical revisions for deplacements / total PEEK	1.33	0	0	0	NA	0
Total PEEK hydrocephalus (N.)	NA	NA	NA	7	NA	0
% PEEK hydrocephalus on total implants	NA	NA	NA	10.61	NA	0

Surgical revision for PEEK hydrocephalus (N.)	NA	NA	NA	7	NA	0
% of surgical revisions for PEEK hydrocephalus	NA	NA	NA	100	NA	0
% surgical revisions for hydrocephalus / total PEEK	NA	NA	NA	10.61	NA	0

Table III.—Overall complications reported in the studies selected for titanium group.

	Honeybul (P)[11]	Lindner (P)[10]	Wiggins (P)[35]	Williams (R)[36]	Mukherjee (R)[37]	Kung (R)[38]	Hill (R)[39]
	2017	2017	2013	2015	2014	2012	2012
Total titanium (N.)	36	26	127	151	174	40	95
% Titanium on total cases	56.25	50	100	100	100	100	100
Male	24	15	NA	107	NA	29	41
Female	12	11	NA	44	NA	11	51
Average age	45	53.1	43	38	NA	44.63	46
Follow-up	12	>1	14	21	>24	31.32	42
Centers	2	3	2	1	1	2	1
Total titanium epidural hematomas (N.)	5	2	5	6	6	0	6
% Titanium epidural hematomas on total titanium implants	13.89	7.69	3.94	3.97	3.97	0	6.3
Surgical revision for titanium epidural hematoma (N.)	2	0	2	5	5	0	4
% of surgical revisions / titanium epidural hematoma	40	0	40	83.33	83.33	0	66.67

% surgical revisions for epidurals / total titanium	5.55	0	1.57	3.31	3.31	0	4.21
Total titanium fluid collections (N.)	0	0	2	23	2	0	11
% fluid collections on total HA implants	0	0	1.57	15.23	1.15	0	11.58
Surgical revision for fluid collections (N.)	0	0	2	1	2	0	2
% of surgical revisions for fluid collections	0	0	100	4.35	100	0	18.18
% surgical revisions for fluid collections / total	0	0	1.57	0.66	1.15	0	2.1
Total infections (N.)	2	9	19	7	15	2	12
% HA infections on total implants	5.56	34.62	14.96	4.63	8.62	5	12.63
Surgical revision for infections (N.)	1	5	18	6	12	0	8
% of surgical revisions for infections	50	55.56	94.74	85.71	80	0	66.67
% surgical revisions for infections / total	2.78	19.23	14.17	3.97	6.9	0	8.42
Total fractures (N.)	0	NA	2	0	0	0	0
% fractures on total HA implants	0	NA	0.79	0	0	0	0
Surgical revision for fractures (N.)	0	NA	1	0	0	0	0
% of surgical revisions for fractures	0	NA	0	0	0	0	0

% surgical revisions for fractures / total	0	NA	0	0	0	0	0
Total titanium prosthesis deplacement (N.)	0	NA	1	0	0	0	1
% Titanium prosthesis deplacement on HA implants	0	NA	0.79	0	0	0	1.05
Surgical revision for titanium prosthesis deplacement (N.)	0	NA	0	0	0	0	1
% of surgical revisions for titanium prosthesis deplacement	0	NA	0	0	0	0	100
% surgical revisions for deplacements / total titanium	0	NA	0	0	0	0	1.05
Total titanium hydrocephalus (N.)	0	NA	1	NA	NA	0	0
% Titanium hydrocephalus on total implants	0	NA	0.79	NA	NA	0	0
Surgical revision for titanium hydrocephalus (N.)	0	NA	1	NA	NA	0	0
% of surgical revisions for titanium hydrocephalus	0	NA	100	NA	NA	0	0
% surgical revisions for hydrocephalus / total titanium	0	NA	0.79	NA	NA	0	0

Table IV.—Overall complications reported in the studies selected for HA group.

	Still (P)[40]	Fricia (P)[41]	Lindner (P)[10]	Moles (P)[42]	Iaccarino (P) [2015]	Ono (R)[43]	Staffa (R)[44]	Staffa (R)[45]
	2018	2018	2017	2017	2015	2017	2012	2007
Total HA (N.)	109	149	26	48	50	41	60	25
% HA on total cases	100	100	52	52.2	52.08	100	100	100
Male	44	103	16	38	35	21	NA	18
Female	65	46	10	10	15	20	NA	7
Average age	45.2	37.4	48.6±15.4	39	NA	65.3	35.8	37
Follow-up	>6	>6	6	24	6	30	24	30
Centers	1	2	3	1	4	1	8	
Total HA epidural hematomas (N.)	1	1	9	3	0	NA	0	NA
% HA epidural hematomas on total HA implants	0.9	0.67	34.62	6.3	0	NA	0	NA
Surgical revision for HA epidural hematoma (N.)	1	0	5	0	0	NA	0	NA
% of surgical revisions / HA epidural hematoma	100	0	83.33	0	0	NA	0	NA
% surgical revisions for epidurals / total HA	0.9	0	19.23	0	0	NA	0	NA

Total HA fluid collections (N.)	0	2	4	0	0	NA	5	NA
% HA fluid collections on total HA implants	0	1.34	15.38	0	0	NA	8.33	NA
Surgical revision for HA fluid collections (N.)	0	0	0	0	0	NA	0	NA
% of surgical revisions for HA fluid collections	0	0	0	0	0	NA	0	NA
% surgical revisions for fluid collections / total HA	0	0	0	0	0	NA	0	NA
Total HA infections (N.)	15	10	2	6	1	2	1	0
% HA infections on total HA implants	13.8	6.71	7.7	12.5	2	4.88	1.67	0
Surgical revision for HA infections (N.)	14	7	2	4	1	1	1	0
% of surgical revisions for HA infections	93.3	70	100	66.67	100	50	100	0

% surgical revisions for infections / total HA	12.8	4.7	7.7	8.33	2	2.44	1.67	0
Total HA fractures (N.)	0	3	0	10	1	0	3	1
% HA fractures on total HA implants	0	2.01	0	20.8	2	0	5	4
Surgical revision for HA fractures (N.)	0	1	0	3	1	0	0	0
% of surgical revisions for HA fractures	0	33.33	0	30	100	0	0	0
% surgical revisions for fractures / total HA	0	0.67	0	6.3	50	0	0	0
Total HA prosthesis deplacement (N.)	5	1	7	5	0	0	0	0
% HA prosthesis deplacement on HA implants	4.6	0.67	26.92	10.41	0	0	0	0
Surgical revision for HA prosthesis deplacement (N.)	0	1	0	3	0	0	0	0

% of surgical revisions for HA prosthesis deplacement	0	100	0	60	0	0	0	0
% surgical revisions for deplacements / total HA	0	0.67	0	6.25	0	0	0	0
Total HA hydrocephalus (N.)	4	1	NA	NA	NA	NA	0	NA
% HA hydrocephalus on total implants	3.7	0.67	NA	NA	NA	NA	0	NA
Surgical revision for HA hydrocephalus (N.)	4	0	NA	NA	NA	NA	0	NA
% of surgical revisions for HA hydrocephalus	100	0	NA	NA	NA	NA	0	NA
% surgical revisions for hydrocephalus / total HA	3.7	0	NA	NA	NA	NA	0	NA

Table V.—Relevant parameters in all multicentric studies.

Complication	Presence	Titanium	Peek	HA	Total
Infections	Yes	32 (13.97%)	13 (7.18%)	14 (4.91%)	59
	No	197 (86.03%)	168 (92.82%)	271 (95.09%)	636

	Total	229	181	285	695
Surgical revision for infections	Yes	24 (10.48%)	12 (6.63%)	11 (3.86%)	47
	No	205 (89.52%)	169 (93.37%)	274 (96.14%)	648
	Total	229	181	285	695
Prosthesis deplacement	Yes	1 (0.44%)	1 (0.55%)	9 (3.16%)	11
	No	228 (99.56%)	180 (99.45%)	276 (96.84%)	684
	Total	229	181	285	695

Table VI.—Relevant parameters in all prospective studies.

Complication	Presence	Titanium	HA	PMMA	Total
Infections	Yes	30 (15.87%)	34 (8.90%)	3 (5.17%)	67
	No	159 (84.13%)	348 (91.10%)	55 (94.83%)	562
	Total	189	382	58	629
Surgical revision for infections	Yes	24 (12.70%)	28 (7.33%)	2 (3.45%)	54
	No	165 (87.30%)	354 (92.67%)	56 (96.55%)	575
	Total	189	382	58	629
Fractures	Yes	2 (1.06%)	14 (3.66%)	0 (0.00%)	16
	No	187 (98.94%)	368 (96.34%)	58 (100.00%)	613
	Total	189	382	58	629
Surgical revision for fractures	Yes	1 (0.53%)	5 (1.31%)	0 (0.00%)	6
	No	188 (99.47%)	377 (98.69%)	58 (100.00%)	623
	Total	189	382	58	629
Prosthesis deplacement	Yes	1 (0.53%)	19 (4.97%)	0 (0.00%)	20

	No	188 (99.47%)	363 (95.03%)	58 (100.00%)	609
	Total	189	382	58	629
Surgical revision for prosthesis deplacement	Yes	0 (0.00%)	4 (1.05%)	0 (0.00%)	4
	No	189 (100.00%)	378 (98.95%)	58 (100.00%)	625
	Total	189	382	58	629

Table VII.—Relevant parameters in prospective multicentric studies.

Complication	Presence	Titanium	HA	Total
Infections	Yes	30 (15.87%)	13 (5.78%)	43
	No	159 (84.13%)	212 (94.22%)	371
	Total	189	225	414
Surgical revision for infections	Yes	24 (12.70%)	10 (4.44%)	34
	No	165 (87.30%)	215 (95.56%)	380
	Total	189	225	414
Prosthesis deplacement	Yes	1 (0.53%)	9 (4.00%)	10
	No	188 (99.47%)	216 (96.00%)	404
	Total	189	225	414

5.3 Arthrogenic human synovial cysts: immunohistochemical profile of IL-1β, IL-6, TNF-α

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Article type: ORIGINAL ARTICLES
Submitted: 2019-10-28
Accepted: 2019-11-28
Published online: 2020-02-20
This article has been peer reviewed and published immediately upon acceptance.

Articles in "Folia Morphologica" are listed in PubMed.

Abstract

Synovial cysts are currently classified as degenerative lesions affecting the joint capsule or adjacent structures. In our study we describe the results obtained in an immunohistochemical study
comprising 18 patients with synovial cysts, performed to evaluate the pathophysiological role of some inflammatory cytokines such as: IL-1β, IL-6 and TNF-α. Results showed an over-expression of TNF-α, IL-1β and IL which appears to be involved in the onset and progression of the disease. At the present time it is not possible to affirm that these molecules play a direct role also due to the absence of further and more specific investigations. The authors therefore hypothesize that inhibition of inflammation may have a significant role in the pathogenesis and regression of synovial cysts. Hence, these inflammatory cytokines may be considered potential therapeutic targets. The development

of synthetic inhibitors of these inflammatory factors could lead to a reduction in the intensity of inflammation, thus inhibiting the onset and development of the disease.

Introduction

Synovial cysts (also known as "ganglion", "synovial ganglion", "arthrogenic cysts") are benign neo-formations of the soft tissues which generally originate from the joint capsule or tendon sheath and contain fluid gelatinous material, usually appearing on the back of the wrist. Sometimes these cysts may involve neural structures, as in cases of peroneal nerve [1] or lumbar roots [2] involvement. Arthrogenic cysts are cysts that occur at the level of the joint capsule. The most frequent location is at the wrist. Since the joints are completely wrapped in a fibrous tissue (capsule) that favors the movements' fluidity, a thinner capsular wall is responsible for a possible traumatic damage and so the cyst may develop in the joint. A herniation of the capsule occurs and it tends to move towards the superficial tissues and to form a revolving structure that we call cysts [3, 4]. The mechanism that gives rise to these cysts is still not clear. Synovial cysts are mostly found in young athletes or workers who use the wrist and hand joints a lot. In many cases synovial cysts are the result of joint inflammation, arthrosis or previous trauma. However, the exact role of inflammation in this process has not yet been studied in detail. The synovial fluid contains inflammatory factors such as cytokines, prostaglandins and proteases. Previous studies have shown that angiogenic factors are released during the formation of the synovial cysts, suggesting a possible correlation between the proliferation of new vessels in synovial structures and the chronic inflammatory process that induces the progression of synovial cysts [2, 5, 6]. However, to date, no previous studies have analyzed the modulation of the inflammatory process in the regression of synovial cysts. It has been shown that in the spinal joint tissue the induction of type 2 cyclooxygenases (COX-2) and phospholipase A2 stimulates the biosynthesis of different inflammatory mediators from synovial chondrocytes (chondrocytes from synovial joints), such as prostaglandin E2, interleukins (IL-1, IL-6 , IL-8) and granulocyte-macrophage colony–stimulating factor (GM-CSF)[7]. Cox-2 inhibitors have been shown to reduce synovitis, leukocyte infiltration and synovial hyperplasia in animal models, reducing the expression of IL-1β, TNF-α and IL-6 [8, 9]. Our study is based on previous experimental data that support the role played by inflammatory cytokines and growth factors in the development of arthrogenic synovial cysts. In the light of the data reported in the literature we hypothesize that inhibition of inflammation may play a significant role in the destiny and/or regression of arthrogenic synovial cysts. The aim of the present study was to evaluate the pathophysiological role of some inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, in tissue samples of synovial cysts or

tenosynovitis, obtained by surgical removal near a wrist joint. The main purpose of this was to evaluate the expression levels and localization of inflammatory cytokines by immunohistochemical analysis to identify their involvement in the pathology and to evaluate the possible modulation of these factors as a potential therapeutic target.

Materials and methods

Clinical evaluation

Written informed consent concerning the donation of human tissues was provided by patients prior to tissue acquisition, following the protocol for the acquisition of human tissues of the Ethical Committee of our University Hospitals which approved the study protocol. All specimens were acquired according to the principles of the Helsinki Declaration. Eighteen patients were included in the study, aged between 11 and 56 years (11 males and 7 females), undergoing surgical treatment for the removal of wrist synovial cysts, in the Orthopedic Unit of the S. Andrea Hospital in Rome. Control samples (2 specimens for each tissue fragment), characterized by normal palmar fascia tissues, were collected from patients undergoing hand surgery for Carpal Tunnel Syndrome (CTS). Patients with concomitant neoplastic, infectious, autoimmune diseases, peripheral vascular disorders or who had performed anti-inflammatory therapy in the six months prior to the operation were excluded. During excision, apart from anaesthesia, no other chemical products or pharmaceutical drugs were administered to the patients. Samples were fixed in formalin and embedded in paraffin to be processed for histological staining and immunohistochemistry. The sections were subjected to Hematoxylin & Eosin and Masson's Trichromic staining.

Immunohistochemistry

The immunohistochemical analysis was conducted using the ABC/HRP technique (avidincomplexed with biotinylated peroxidase) on 4μm thick paraffin sections which were cut using a rotative microtome. These sections were deparaffinized and hydrated through decreasing ethanol series to distilled water, then subjected to microwave irradiation and immersed in citrate buffer (pH= 6) twice for 5 minutes each time. Subsequently, endogenous peroxidase activity was quenched using 0.3% hydrogenous peroxide in methanol for 30 minutes. To evaluate the immunolocalization of IL-1β, TNF-α and IL-6, the following antibodies were employed: i) rabbit anti-IL-1β polyclonal antibody (1:50, Santa Cruz Biotechnology, Santa Cruz, CA, USA); ii) mouse anti-TNF-α monoclonal antibody (1:100, Santa Cruz Biotechnology, Santa Cruz, CA, USA); iii) rabbit anti- IL- 6 polyclonal antibody (1:200; Santa Cruz Biotechnology, Santa Cruz, CA, USA). Incubation with the primary

antibodies was performed overnight at 4° C. Optimal antibody dilution and incubation times were assessed in preliminary experiments. As negative control, the primary antibodies were omitted. After exposure to the primary antibodies all slides were rinsed twice in phosphate buffer (pH=7.4) and incubated for 1 hour with the appropriate secondary biotinylated antibody at the final dilution of 1:200. The secondary biotinylated antibodies against rabbit and mouse immunoglobulins were purchased from Abcam (biotinylated goat anti-mouse antibody and biotinylated goat anti-rabbit antibody). The slides were then incubated with peroxidase-conjugated avidin (Vector laboratories, Burlingame, CA, USA, Vectastain Elite ABC kit Standard*PK 6-100) for 30 min. Slides were washed in phosphate buffer (pH=7.4) and treated with 0.05% 3,3- diaminobenzidine (DAB) and 0.1% H2O2. Finally, sections were counterstained with Mayer's hematoxylin and dehydrated rapidly. The staining assessment was made by three experts. The intensity of the immune reaction was assessed microdensitometrically using an IAS 2000 image analyzer (Delta Sistemi, Rome, Italy) connected via a TV camera to the microscope. Twelve 100μm2 areas were delineated in each section by measuring the diaphragm. The system was calibrated taking the background obtained in sections exposed to non-immune serum as zero.

Statistical analysis

Statistical analysis was performed with the Student's t-test, using the GraphPad Prism (La Jolla, CA). A p-value<0.05 was considered for statistical significance.

Results

The histopathological alterations caused by human arthrogenic synovial cysts were evaluated using the immunohistochemical technique. Immunohistochemical experiments have made it possible to visualize the distribution and localization of the cytokines analyzed in the tissue samples obtained by surgical removal from patients with arthrogenic synovial cysts (Table I). Through hematoxylin / Eosin staining it was possible to detect, in the pathological tissues, the myofibroblastic proliferation site (Fig. A1-A3), not present in the control tissue (Fig. A4). In the pathological tissue (Fig. A1-A3) a thickening of fibroblasts and myo-fibroblasts was visible with areas of complete cellular overlapping. This tissue morphology is not present in normal tissue (Fig. A4), in which only connective tissue with dispersed fibroblasts and small blood vessels can be observed. Figures B1-B3 describe the immunohistochemical expression of interleukin 1β (IL-1β) in pathological samples, demonstrating positive reactions in the cytoplasm of myo-fibroblastic cells and in the extracellular matrix. IL-1β is completely absent in the extracellular matrix of the palmar control fascia specimens (Fig B4). Moreover, this pro-inflammatory cytokine is highly

expressed at the level of the capillary endothelium, near the synovial cysts. Interleukin 6 (IL-6) is appreciable in extracellular matrix, both in proliferating myo-fibroblasts and in fibroblasts at the level of proliferative nodules in patients affected by arthrogenic synovial cysts (Fig. C1). In the normal tissue of palmar fascia IL-6 appears to be completely absent at the level of the loose connective tissue, but moderately present in the endothelial cells of the blood vessels and in the fibroblasts scattered in the connective tissue (Fig. C2). Unlike the other cytokines, IL-6 shows an appreciable localization in normal fibroblasts (Fig. C1) and a more evident cytoplasmic localization in the pathological ones (Fig. C2). This cytokine appears to be involved in the inflammatory process that leads to the activation of the fibrotic process. Therefore, IL-6 appears to be synthesized in response to TGF-β1 and acts by enhancing the proliferation and differentiation of fibroblasts into myofibroblasts with deposition of amorphous substance in association with TGF-β1. Tumor necrosis factor α (TNF-α) is expressed in the extracellular matrix of the myo-fibroblastic tissueat the proliferation site observed in patients with synovial cysts (Fig. D1). TNF-α is present in pathological myo-fibroblasts and in capillary endothelial cells (Fig. D1). In the loose connective tissue of the normal palmar fascia this inflammatory factor is however moderately positive in the cytoplasm of fibroblastic cells and in the extracellular matrix (Fig. D2). This growth factor is also strongly expressed in the cytoplasm of secreting sweat glands (Fig. D2) in the dermis near the pathological proliferative nodules.

Discussion

Arthrogenic synovial cysts are a benignly progressing fibro-proliferative disorder which often lead to severe functional damage. The lack of knowledge related to the etiopathogenesis of the disease has meant that a specific therapy is not currently available until now. Therefore, it is difficult to prevent its onset or to avoid its recurrence after surgical excision. The absence of valid therapeutic targets has led to the development of empirical therapies, such as local injection of steroids [10]. Inflammation plays a fundamental role in the onset of fibrosis and this finding is confirmed by the presence of proinflammatory cytokines [11]. In physiological conditions of wound healing or tissue repair activation of the fibrotic process occurs. During this process fibroblastic cells may differentiate into myo-fibroblasts, because their contractile activity is essential for tissue remodelling. The formation of myo-fibroblasts, controlled by a variety of growth factors and numerous mechanical stimuli, leads to an excessive deposition of extracellular matrix. Their action ends when the tissue is completely repaired or reabsorbed. In some pathological conditions the contractile activity of myo-fibroblasts persists and leads to tissue deformation [12]. IL-1β, an important pro-inflammatory cytokine, is involved in “in vitro” fibroblastic

proliferation through the induction of the expression of transcriptional factors such as c-fos, c-jun and c-myc [13]. The excessive expression of IL-1β alone could be responsible for the local fibroblastic proliferation seen in the active phase of the disease. IL-1β seems to have an important function in the activation and feeding of the inflammatory process, inducing the synthesis of other cytokines such as IL-6 and IL-2, interferons or chemokines, which are able to attract macrophages and granulocytes towards the site of inflammation. It seems probable that the mitogenic effect of IL-1β is enhanced by the co-expression of other factors such as TGF-β and PDGF-α/β. The combined expression of these growth factors are probably responsible for fibroblastic proliferation and excessive deposition of an amorphous substance and accumulation of synovial fluid, a condition typical of the disease. In our experiments we also evaluated the level of IL-6 expression. This cytokine is directly involved in the activation of the initial inflammatory process which subsequently leads to fibrosis. The pro-inflammatory cytokine IL-6 plays an important role in the regulation of inflammation and acts in association with TGF-β1, thus leading to an increased profibrotic response[14, 15]. IL-6 acts by enhancing the TGF-β1 signal by increasing endocytosis mediated by non-lipid endosomes. This consequence is due to internalization of the TGF-β1 receptors as a result of binding of their ligand through endocytosis mediated by caveolin lipid vesicles and by non-lipid vesicles, although the TGF-β1 signal increases when the receptor endocytosis is mediated by non-lipidic vesicles. Therefore, IL-6 and TGF-β1 act synergistically, causing an increase in the expression of proinflammatory cytokines that appear to be the primary cause of the onset of the disease. Verjee et al. [16] reported that TNF-α at low concentrations induce myo-fibroblastic contraction, while at high levels it induces reduction or complete inhibition of myo-fibroblastic contraction. It seems that the action of TNF-α depends strictly on the TNFR
receptor type: TNFR2 causes fibroblastic proliferation, while TNFR1 activates programmed cell death. TNF-α could be considered a possible therapeutic target for the treatment of the disease in the primary stages or in preventing relapses following surgical removal. In our experimental study we found that TNF-α showed a greater localization in pathological fibroblasts. Therefore, this factor appears to be directly involved in the fibrotic reaction and its action depends exclusively on its TNFR2 receptor, which is strongly expressed in pathological conditions. Based upon our preliminary results, local injections of anti-TNF-α drugs could be useful in preventing the progression of the disease or avoiding its recurrence after surgical treatment. During the involutive phase a high ratio of collagen III on collagen I was detected, differently from the normal physiological condition [17]. These experimental results suggest, therefore, a possible application of these pro-inflammatory factors in the identifying the degree of disease progression and in the use of some of these markers as

prognostic factors in the follow-up of patients undergoing surgical resection of synovial cysts. Innovative therapies could be characterized by the combined use of specific inhibitors of the factors TNF-α, IL-1β and IL-6 and their receptors in order to inhibit the progression of the disease through inactivation of the fibrotic process.

Acknowledgments

This work was supported by a grant of the "Enrico ed EnricaSovena" Foundation, Italy.

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FIGURES:

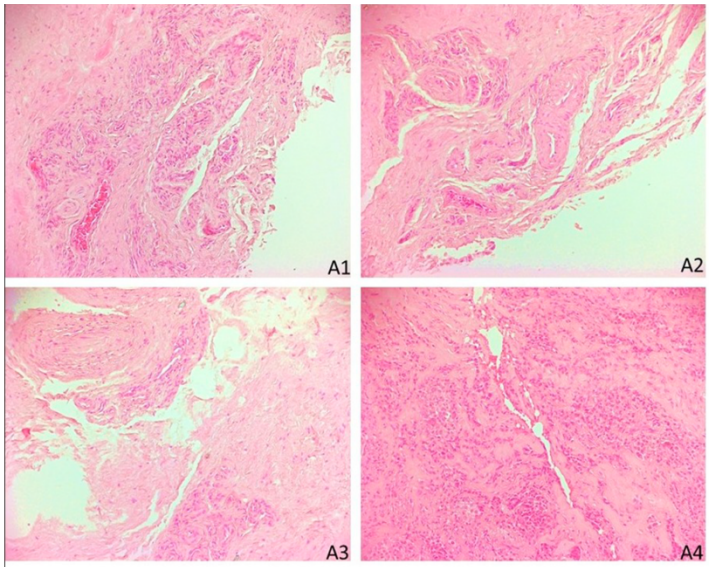

Figure A. Photomicrograph of histological preparations obtained by the HEMATOXYLIN/ EOSIN staining method. Fig. A1 –A3 Proliferation myofibroblast nodules (asterisks)

obtained by surgical removal from a patient with synovial cyst (10X); Fig. A4 normal palmar band consisting exclusively of connective tissue with fibroblasts and blood vessels (10X).

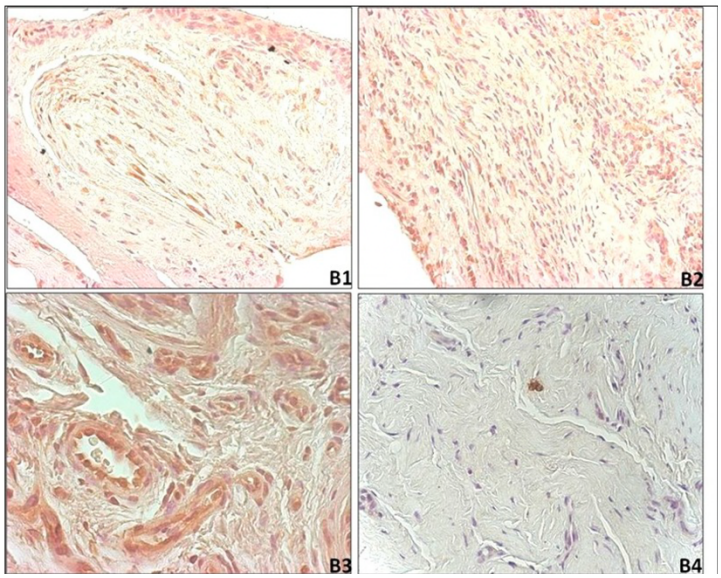

Figure B. Photomicrographs of the immunohistochemical reaction for the inflammatory cytokine IL-1β. Fig. B1 –B3 Pathological tissue in which IL-1β is present in the extracellular matrix and in the cytoplasm of fibroblasts and myofibroblasts and in the endothelium of capillaries (B1, B2, 20X; B3, 40X). Myofibroblasts nodules (asterisks). Fig. B4 control tissue (20X).

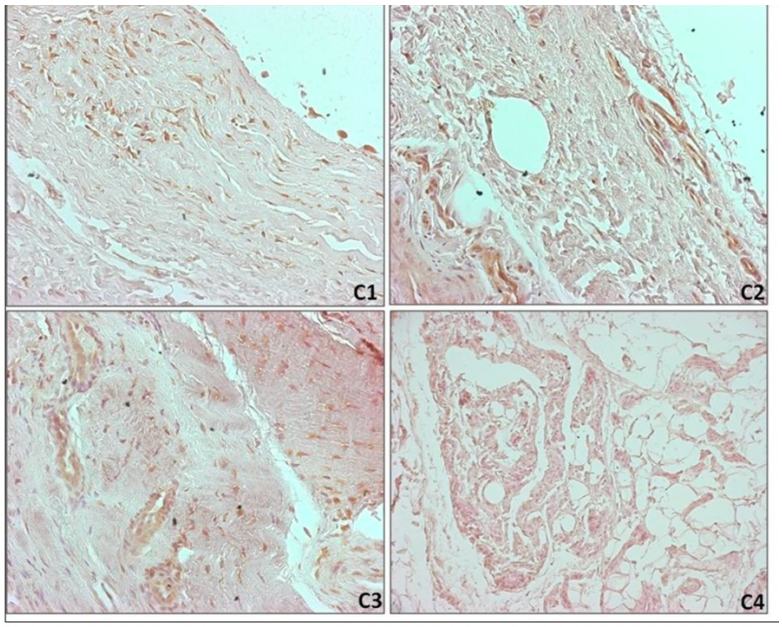

Figure C. Photomicrographs of the immunohistochemical reaction for the cytokine IL-6. Fig. C1- C3 Pathological tissue in which IL6 is expressed at the level of proliferative nodules (asterisks- C1, C2, C3, 20X). Fig. C4 control tissue (10X).

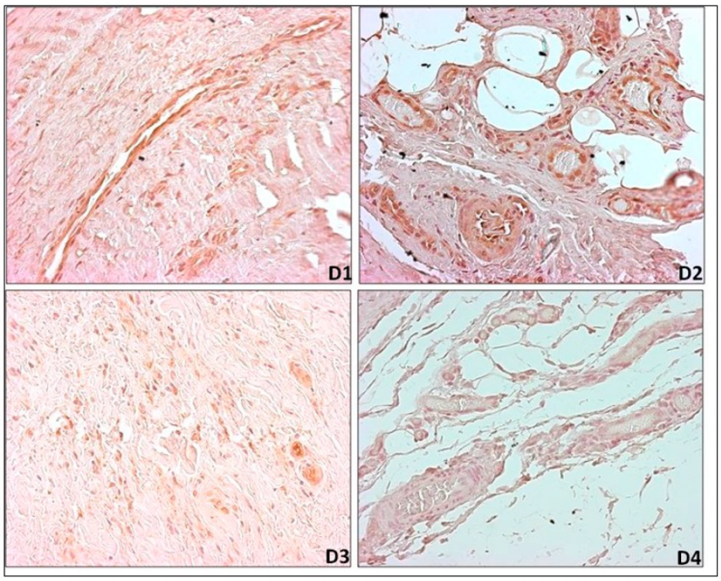

Figure D. Microphotographs of the immunohistochemical reaction for the proinflammatory cytokine TNF-α expressed in pathological myofibroblasts and in capillary endothelial cells (D1, D2, D3, 20X). Myofibroblasts nodules (asterisks). Fig. D4 control tissue (20X).

	synovial cysts (%) n=15	control specimens (%) n=15	p-value
IL-1β	65.27 ± 12.91	12.61 ± 5.51	p < .00001
IL-6	60.46 ± 10.70	11.66 ± 4.96	p < .00001
TNF-α	61.80 ± 10.22	13.13 ± 5.81	p < .00001

Table 1. Expression levels of IL-1β, IL-6, TNF-α in synovial cysts and control specimens, and respective levels of statistical significance (t-test).
The results were considered as statistically significant when P-value<0.05
synovial cysts (%)

5.4 Management of Gunshot wound to the lumbosacral spine in a 17-year-old girl without neurological impairment. Case description.

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Case report
J Biol Regul Homeost Agents.
2020 Jul-Aug;34(4 Suppl. 3):1-5.
Congress of the Italian Orthopaedic Research Society.

Abstract

We report the case of a young girl (17 year old) wounded by an accidental gunshot. The bullet entered through the skin midline over the navel area, passed through the stomach, peritoneum, perforated the cava vein and, breaking the right pedicle of L4, moved inside the vertebral canal stopping just in front of the body of S2. For the sudden onset of acute abdomen due to a retroperitoneal hematoma, the patient underwent emergent explorative laparotomy with the evacuation of the hematoma and the suture of the perforated cava vein, of the peritoneum and of the stomach. No neurological deficits were observed after the gunshot. Two weeks later the patient underwent spinal surgery to remove bullet from the spinal canal, which was performed successfully without any instrumentation and without the onset of neurological signs and symptoms or surgery-related complications. Patient was discharged on day 9 after surgery in good general conditions.

Introduction

Spinal cord gunshot injuries (GSI) are penetrating spinal trauma, which leads to significant morbidity and mortality. Gunshot wounds (GSWs) represent an increasing cause of spinal cord in injury in the urban setting and the incidence account for 16% of all spinal cord injury, ranging from 13 to 44% depending on the country **[1-3]**. The 78 to 94% of these patients are yang (30 years old) and most of them and most suffer from secondary neurological impairment due to spinal cord trauma. **[2,4].**

GSWs injuries of the spine are classified in three main types accordingly to the position of the projectile relative to the spine and the involvement of internal organs.
In GSWs type I, or transfixing, small fragments are found inside the canal. This is the most frequent type of injury (>70%).
In GSWs type II or intracanal, the whole projectile is inside the canal, comprising 20.4% of cases
GSWs types III are intervertebral lesions because the bullet is inside the intervertebral disc space. In these subtypes perforation of abdominal organ or hemopneumothorax can occur more frequently (GSWs type III type A-B). **[2].** The incidence of concomitant lesions of vital organs is 20%. **[5].**
Vital organs are mainly involved in case of lumbosacral regions GSW whereas massive bleeding may endangers the life of patient therefore should be promptly identified and treated. **[2].**
The management of GSWs of the spine is a controversial issue and both conservative and surgical treatment has been widely discussed **[2]**.
The severity of neurological impairment, according to the American Spinal Injuries Association (ASIA A-C), the level of spinal cord injuries (Thoracic > Cervical > Lumbosacral/Cauda-equina) and the type of cervical or thoracolumbar injury, according to Thoracolumbar Injury Classification and Severity Scale (TLICS) as well as Cervical Spine Injury Classification System (SLIC) have been investigated as possible outcome predictors **[6]**.
In absence of neurological or vital organs impairment, septic and long term complications such as chronic pain or bullet migration should be considered and eventually treated.
We present a 17-year-old girl patient with GSW type II lumbosacral injury with vital organs involvement. The bullet caused a stomach and cava vein laceration, a wedge and monolateral pedicle fracture of L4, ending in the spinal canal in proximity of S2.

Description of the case

A 17-year-old girl patient accessed the emergency department (ED) of a suburban hospital with a GSW. At admission vital signs were stable without neurological impairment, (GCS 15, ASIA E). Clinical inspection showed a bullet entry point in the supra-umbilical midline region. Exit point was not visible. Computer tomography scan (CT scan) demonstrated an acute retroperitoneal hematoma, evidence of retained bullet fragment in the vertebral canal in proximity of S2 associated with fracture of right pedicle and wedge of L4. Tetanus prophylactic and broad-spectrum antibiotic therapy were started immediately (Tazobactan 18 g/day, Metronidazole 1,5 g/day, Ceftriaxone 6 g/day). The patient underwent emergent

explorative laparotomy with acute blood loss, treated with blood transfusions. During abdominal surgery an anterior and posterior perforation of the stomach's antrum in the pre-pyloric area were observed as well as peritoneum laceration. The presence of great amount of retroperitoneal blood was intraoperatively showed due to perforation of the anterior wall of the cava vein in proximity of L4. No perforation of bowel or arteries was found. The surgeons could successfully suture all the perforated structures without any complication. After surgery the patient was moved to the intensive care unit (ICU). Neurological status was intact. Antibiotic therapy was stopped 7 days after injury. No fever or infection-related signs or symptoms were observed. About two weeks after surgery the patient suffered from nausea and vomiting which could not lead to a regular alimentation, so she underwent parenteral nutrition. For what concerns other symptoms, she just suffered from slight low back pain; cautiously she did not stand up. Sphincterial functions were intact (anal manometry was normal, urinary catheter was removed on day 11 after laparotomy, replaced immediately for urinary retention and then definitely removed on day 13). One month after injury, the patient was moved to the Spine units of "IRCCS Galeazzi" (Milan, Italy) for removal of the bullet inside the spinal canal. Surgery was performed with patient in prone position after general anaesthesia. Intraoperative landmark was acquired thanks to plain X-ray, which led to precise localization of the bullet. A small skin incision was made, targeted on the acquired landmark. Superficial muscular fascia was dissected and prepared for additional subsequent dura repair. Muscular fibers were dislocated laterally to visualize sacral bone on its paramedian right side; using scalpels, a small bony square area was removed to reveal dura mater. Under the bony layer; blood clots mixed to soft tissue and CSF were found. After accurate dissection and suction of the bloody component, dura mater breakage with CSF leak was recognizable. The laceration of the dura, not clearly visible on preoperative CT scan, was found postero-medially; underneath, the bullet was recognizable, surrounded by blood clots, with the sacral roots beneath. Careful dissection of the bullet from the surrounding anatomical structures was performed. At the end, the bullet was entirely removed. No injuries to the sacral roots were found. Accurate suture of the dura layer with apposition of autologous fat pad, muscular fascia prepared at the beginning and fibrin glue was performed to repair CSF leakage.

No complications were observed after surgery; patient was able to stand up on day 2 and walk without any assistance. She developed no headache or other CSF leakage associated conditions; wound healing was normal considering age and clinical status and she did not suffer from any sphincterial disturbance. It was not planned to treat the fracture of L4 considering it stable and unilateral, without spinal canal involvement.

The patient was discharged after 5 weeks from trauma clinically and neurologically intact.

Follow up at 6 years after removal of the bullet is normal: patient is healthy, with no neurological deficits. A CT scan and a MRI of the spine showed normal progress after surgery.

Discussion

Although surgical removal of retained bullet into the spinal canal/dural sac is still controversial, the demand of surgical care is increasing in the last years **[7].**

Despite vascular complications or vital organs injuries are considered for an emergency management, spinal involvement is not usually life-threatening and often an early decompression does not mean a guaranteed neurological recovery **[6, 8-9].**

The only absolute early surgical indications are represented by presence of CSF fistula, documented neurological impairment progression associated with radiological evidence of neurological compressions and spinal instability. **[4].**

Where some authors suggest to not proceed to bullet removal because of surgery-related risks (infections, roots damages), other authors are favorable to the surgery considering the risk of neurological deterioration and formation of sterile abscess or granuloma in the bullet area **[10-12].**

In absence of neurological involvement surgical management is even more controversial, but the impact of possible delayed complications on the morbidity and mortality of these patients should be carefully considered.

Infections (superficial or deep, meningitis, abscess) or bullet ferromagnetic proprieties or its migration in the dural sac may represent potential cause of morbidity and mortality; likewise direct spinal cord injury **[7].**

Migration of the bullets inside the spinal canal many years after being shot is not so uncommon and may cause late onset of pain, discomfort or neurological deficits **[10-12].**

According to literature some cases of delayed cauda equina syndrome due to migratory bullet were recorded and in these cases the authors recommended surgical management **[13-15]**. A late surgery might be associated to higher intraoperative risks and more invasive surgical decompression to remove the bullet.

Moreover, in presence of intradural bullet fragment, a dural tear should be suspected, even if is not recognised on preoperative CT scan examination. **[16]**

In our case an early open posterior approach to the lumbosacral region was performed in order to decompress spinal canal and to remove the bullet fragment. During surgery we repaired a dural breakage with CSF leakage that was undiagnosed on preoperative radiological imaging, preventing a delayed CSF leak.

Our purpose was to avoid delayed complications as persistent pain, delayed neurological symptoms onset, infection or fragment dislocation.

Therefore for these reasons and for the young age of our patient, despite she was neurologically intact an early surgery has been preferred.

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Figures

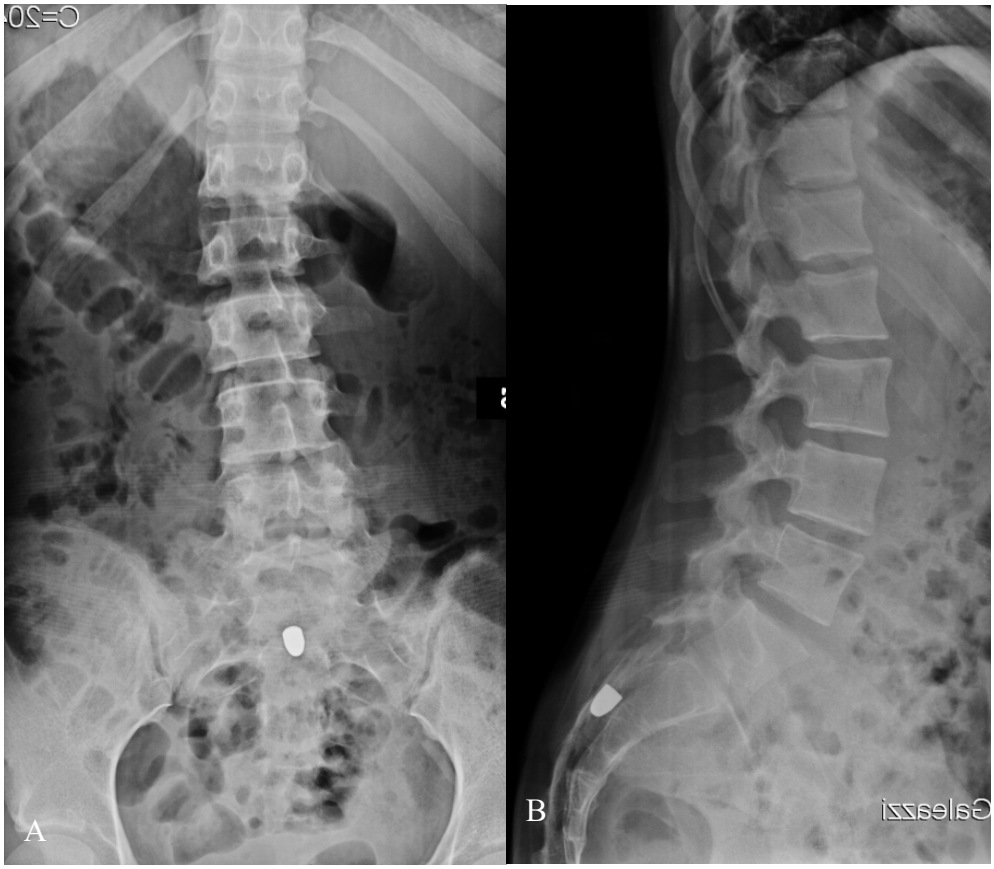


FIG 1: (A,B) Frontal and Lateral X-Rays showed a foreing body in the spinal canal in proximity of S2.

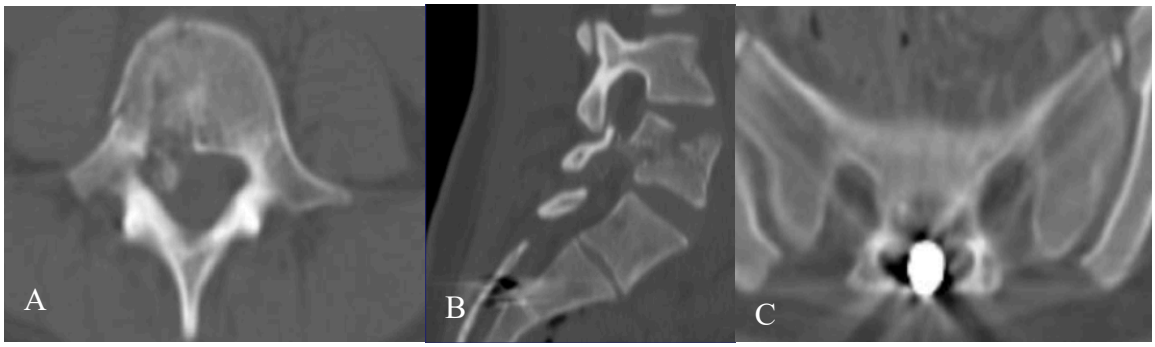
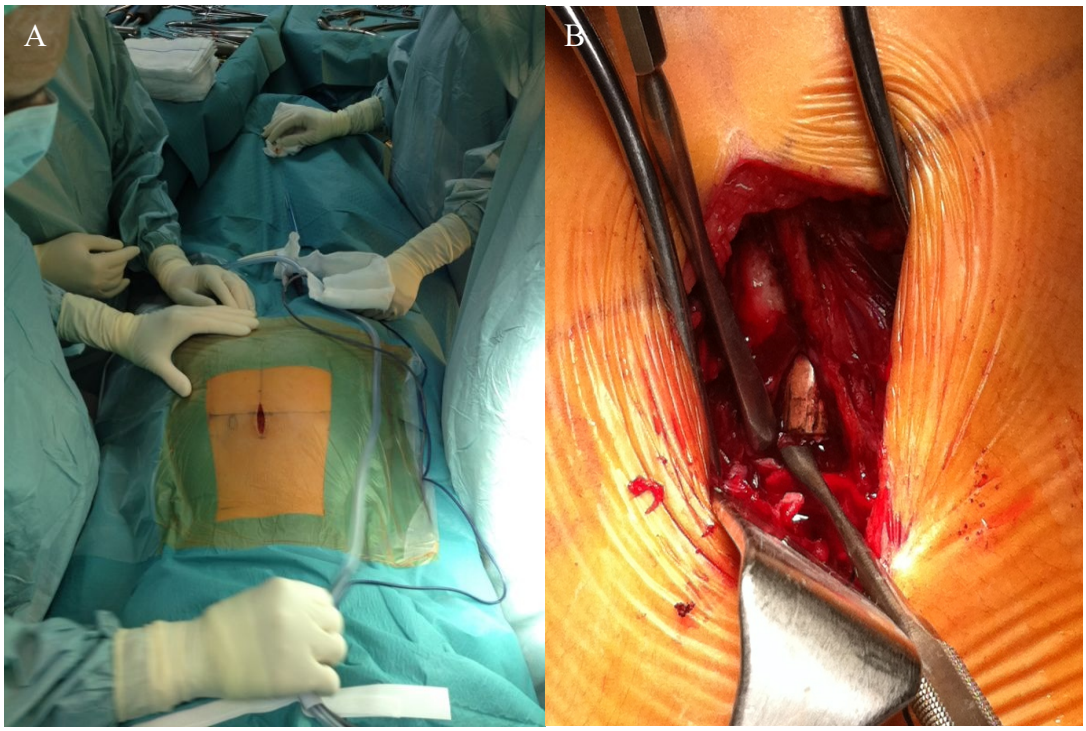


FIG 2: A,B: axial and sagittal CT scan showed fracture of right pedicle and wedge of L4. C: axial view showed intracanal bullet fragment in S2



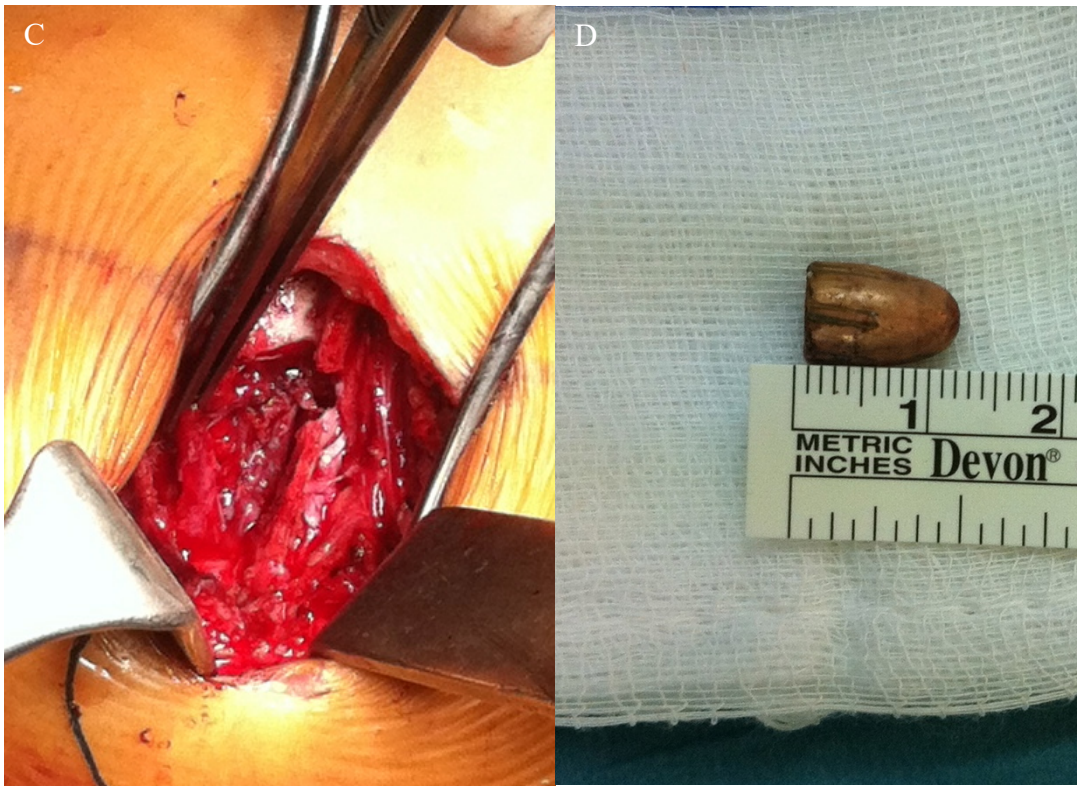


FIG 3: Surgical field before and after removal of bullet fragment

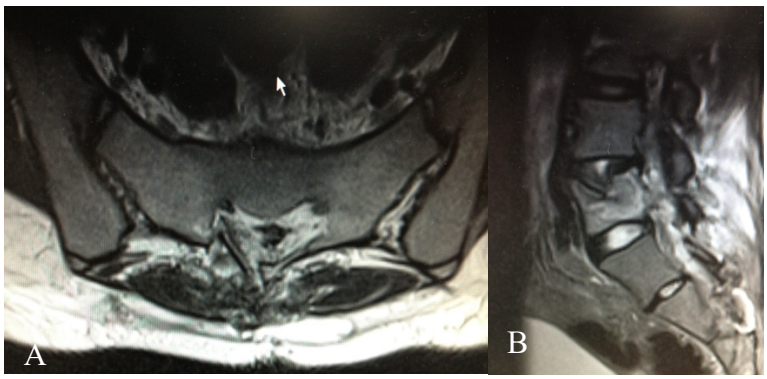


FIG 4: (A,B) axial and sagittal postoperative MRI showed L4 fracture without loss of body height or lumbar alignment and complete sacral canal decompression.

5.5 Congenital instability of cervical spine in a pediatric patient with cleft lip and palate.

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Our reference: INAT 101413
Article reference: INAT_INAT-D-21-00371
Article title: "Congenital instability of cervical spine in a pediatric patient with cleft lip and palate ".
To be published in: Interdisciplinary Neurosurgery: Advanced Techniques and Case Management

ABSTRACT
Introduction
Cervical spine anomalies can coexist with anomalies of the head and neck. The association of cervical vertebrae anomalies (CVA) with cleft lip and palate (CLP) has been described as probably the result of a failure in normal embryological segmentation. The most frequent congenital alterations of cervical spine CLP-related are vertebral fusion (VF) and deficiency of the posterior arch (PAD).
Case Presentation
We report a case of an acute, non-traumatic onset of paraparesis in a 14 years old girl with history of CLP and bilateral conductive deafness. Magnetic resonance (MR) and Computed Tomography (CT) imaging of the cervical spine revealed C4-C5 myelopathy sign and a misunderstood C2-C3 and C5-C6 partial posterior VF. A C2 deficiency of the posterior arch was also present. Dynamic X-Rays showed a junctional instability of C4-C5 metamers. The patient was surgically treated with anterior *cervical* discectomy and fusion (*ACDF*) with immediate improvement of the symptoms.
Conclusions

The new onset of spinal cord involvement in pediatric patients with a history of head and neck developmental disorder could be ascribed to congenital cervical spine malformation and therefore should be detected by appropriated radiological imaging as early as possible to optimize surgical management and reducing the risk of neurological impairment.

Keywords: Cervical vertebrae anomalies (CVA), vertebral fusion (VF), cleft lip and palate (CLP).

Introduction

Congenital anomalies of the cervical spine in pediatric patients are rare conditions that should be early recognized and carefully managed to prevent neurologic impairment. In some cases, cervical spine anomalies are associated with evident organs abnormalities as manifestation of hereditary and systemic diseases. Skeletal dysplasia (i.e. Osteogenesis imperfecta, Neurofibromatosis), connective tissue disorders (i.e. Marfan syndrome), inflammatory arthritis (i.e. juvenile rheumatoid arthritis) or congenital disorders (Klippel-Feil syndrome, KFS) are the commonest and most severe pediatric disorders with involvement of the cervical spine [1-2].

Moreover, cervical anomalies with mild representation can be misdiagnosed if not framed in specific syndromes or in congenital disorders. The association of cervical vertebrae anomalies (CVA) and orofacial abnormalities such as cleft lip and palate (CLP) has been reported since 1965 [3]. Many studies focused on embryogenesis development of the neck and maxillofacial complex have contributed to understand the possible association among cervical anomalies and orofacial and acoustic disorders and to explain the etiology of CLP [3]; however, strong evidence of this association is currently insufficient [4-5].

CLP disorder can result in complications affecting feeding, speech, hearing and psychological development. During childhood, these individuals undergo several procedures to restore normal maxillofacial and functions, and generally are asymptomatic for cervical spine involvement. The cervical spine is generally not screened for associated anomalies and CVA is discovered incidentally during the second or third decade of life [6]. Prevalence of cervical vertebrae anomalies in patients with cleft lip and palate reach 20.3% [7]

The most frequent congenital alterations of cervical spine CLP-related are vertebral fusion (VF) and deficiency of the posterior arch (PAD) [8]. Patients with VF may be predisposed to degenerative changes and hypermobility at segments adjacent to fused vertebrae in adulthood [9].

We report a case of an acute, non-traumatic onset of paraparesis in a misdiagnosed congenital instability of cervical spine in a pediatric patient with cleft lip and palate. To our knowledge this is the first reported case of early occurrence of sudden cervical myelopathy in a patient affected by congenital CLP, bilateral hearing loss and cervical spine anomalies. The aim of this case presentation is to enforce the importance to investigate cervical spine in presence of multiple anomalies of the head and neck, even in non-syndromic patients.

Case report

A young patient of 14 years old presented two acute, non-traumatic onsets of transient para/tetraparesis initially not related to a precise diagnosis. The neurological examination documented impaired sensation below the C5 dermatome with numbness and dysesthesia of the lower limbs and increased muscle hypertonus, and presence of Babinski and Lermitte signs.

Previous surgical procedures of CLP repair (at the age of 2 years old) were reported in patient's clinical history. A bilateral hearing aid device (BiCros system: Bilateral Controlateral Routing of Signal) was applied for a transmissional hearing loss. Genetic evaluation was negative for congenital disorder.

A MRI of brain and cervical spine revealed an increased T2 signal within the cord at C4-C5 (FIG 1). Subsequently CT scan showed a C5-C6 VF previously misdiagnosed as osseous continuities without complete separation at the intervertebral disc. A severe dynamic instability and anterolisthesis of C4, demonstrated by the flexion- extension X rays was the main cause of spinal cord compression (FIG 1). Therefore, an anterior cervical discectomy and fusion of C4-C5 (ACDF) procedure was performed to provide immediate stability to the cervical spine (FIG 2). Fully informed written consent was obtained regarding the risks and benefits of the procedure.

The patient was moved on the surgical table and immobilized with cervical collar. A general anesthesia was performed with endoscopic endonasal intubation to avoid extreme extension of the neck. Patient was then placed in a supine position. Preoperative radiological imaging excluded other anatomical anomalies of the neck and therefore a standard pre-sternocleidomastoid (SCM) muscles transvers skin incision was performed. Intraoperative neuromonitoring was obtained with combined motor and somatosensory evoked potential (SSEP and MEP). The anterior cervical spine was reached from the left side to reduce the risk of recurrent laryngeal nerve palsy (RLNP), as the nerve is more reliably protected within the tracheoesophageal interval on the left side. The treatment for cervical instability aims to obtain spinal cord decompression, correction, and fusion. Once the C4-C5 disc space

was exposed, anterior complete discectomy was completed. An intersomatic titanium cage filled by heterologous bone was implanted to provide intersomatic fusion and anterior listhesis reduction. The cage was fixed with an anterior plate to improve primary stability. At the end of surgery, the C4 listhesis was completely reduced, without neurological or surgical problems.

Postoperative clinical follow-up after 6 and 12 months showed great improvement of myelopathy and absence of any neurological signs (normal muscles tone), and complete recovery of symptoms as numbness and dysesthesia of the lower limbs. The 6 months MRI showed great improvement of radiological signs of spinal cord signal (FIG 3) and the correct alignment of the cervical spine.

Discussion

Nontraumatic congenital cervical spine instability is caused by rare conditions, which sometimes are difficult to diagnose during childhood [2]. Our young patient presented a dynamic cervical instability above a VF. According to the literature, the instability can be triggered by the mechanical stress, which is a consequence of the vertebral fusion. The presence of a rigid segment, associated with ligamentous laxity and immature neck musculature can modify the physiological range of motion of the spinal segment (including 2 vertebral bodies, the intervertebral disc, joints, and ligaments), resulting in instability [10-11]. In our case, a nontraumatic cervical spine instability triggered also neurological impairment. Therefore, a surgical treatment was required to decompress the spinal cord, realign, and fuse the segment of motion. An anterior approach was chosen to achieve direct spinal cord decompression, and consequent progressive neurological improvement. A posterior cervical decompression or fusion in this case was not performed because the anterior approach allowed for the optimal listhesis reduction; moreover, the posterior approach may have led to posterior muscles impairment.

The importance of MRI imaging in the early stage of symptoms onset is crucial. In absence of clear syndromic diseases, other bony pathologies of the spine, such as eosinophilic granuloma or benign osteoblastoma of the spine should be ruled out [12].

Primitive tumors of the spine have usually an history of increasing local pain and progressive neurological impairment. Tumors can lead to vertebral instability mainly due to the osteolitic effect of the tumor cells [12].

The CVA can coexist with development anomalies of the head and neck. According to Samartzis classification [2], the congenital cervical VF can be classified in three types based on level of fusion. Single congenitally fused cervical segment characterizes the type I;

multiple noncontiguous congenitally fused segments characterize the type II, whilst Type III is represented by multiple contiguous congenitally fused cervical segments.

Young subjects with congenitally fused cervical vertebrae present an increased risk of degenerative changes of the contiguous metamers that can lead to myelopathy in adulthood [9].

Several mechanisms of spinal cord injuries have been purposed proposed, such as the coexistence of spinal cord anomalies, or congenital canal narrowing, vertebral instability and vascular dysfunctions [11].

In adult patients, the fused vertebra may contribute to alter the stress forces and/or a degenerative cervical process, thus causing instability [9, 11].

In pediatric population, neurological involvement of the cervical spine is described in patients affected by specific syndromes such the KFS, which is characterized by short and stiff neck, abnormal fusion of at least two vertebrae and low hairline [10]. In these patients neurological changes slowly progress or they can be worsened by minor traumas, especially in presence of occipitocervical abnormalities [11]. Embryogenetic disorder may explain the association of non-syndromic cervical spine and head/neck anomalies [3].

The type of CVA (VF, PAD, vertebral artery canal, anomalies of the anterior arch in C1, odontoid process abnormality), the level (upper or subaxial cervical spine) and the number of involved segments may be associated with different kinds of cleft lip and palate anomalies: isolated CP (ICP); unilateral CLP (UCLP) and bilateral CLP (BCLP). According to the literature, the prevalence of CVA is highest in the UCLP (52.8% of PAD, 33.9% of fusions) and BCLP groups (56.0% of PAD; 32.0% of fusions) [3]. However, no strong relations with types of cleft lip and palate and cervical anomalies have been observed [3]. Moreover, no significant difference in prevalence of CVA between males and females was found [3].

The diagnosis of non-syndromic CLP during childhood is frequently associated with transmissional hearing loss. Despite the higher prevalence of CVA in CLP patients [3], cervical anomalies are not routinely investigated in those subjects, thus increasing the risk of neurological damages.

In this case report (type II of Samartzis classification and bilateral CLP, BCLP) the two noncontiguous C2-C3 and C5-C6 fusions produced a pivot on the C4-C5 “healthy” disc, leading to segmental instability and then to spinal cord progressive injury.

Hence, interbody fusion was necessary to obtain anterior column support and stability. At the last follow-up complete neurological improvement has been observed, probably thank to the young age of our patient.

The study has some limitations; as we could not establish the effective cause of the cervical instability, that could be only postulated according to the literature. Moreover, we did not investigate the interbody fusion by CT scan after surgery, to avoid an excessive radiation exposure for our young patient.

Conclusions

A strong association among cervical anomalies and cleft patients is well known. Therefore, a cervical spine screening by MRI of CLP patients should be advocated to avoid sudden and early spinal cord injury in those subjects. A new onset of neurological symptoms in pediatric patients with a story of CLP, should be detected by radiographic imaging (MRI and cervical X-Rays) as early as possible to optimize management and to reduce the risk of further neurologic impairments.

Funding

The authors have no funding to report for this manuscript.

Authorship contribution statement

Carlotta Morselli: Writing - original draft, review & editing. Patrizia Mancini: review & editing. Agostino Cirullo: Data collection, Writing - review & editing. Laura Mangiavini: Writing - review & editing. Roberto Bassani: Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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FIGURES

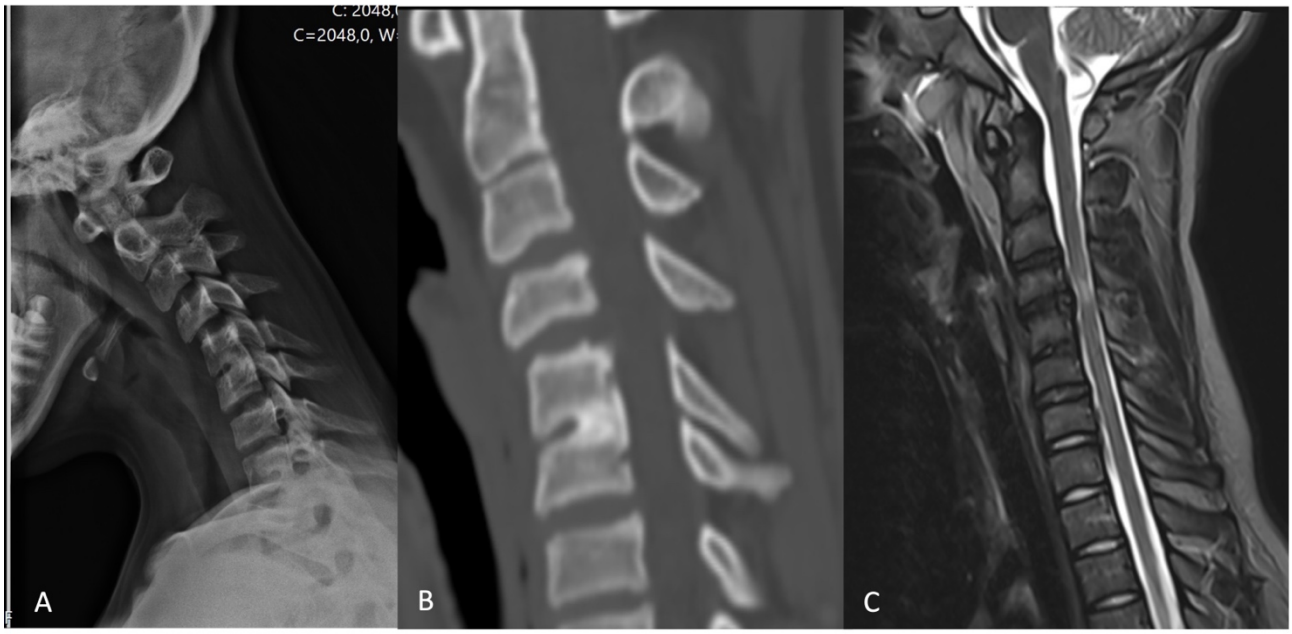

FIG 1: **Preoperative imaging.** A) preoperative Flexion Cervical X-Ray showing C5-C6 posterior vertebral body fusion and C4 anterior listhesis. B) Preoperative sagittal CT-scan that confirm C5-C6 posterior vertebral body fusion and the reduction of C4 listhesis in neutral position.
C) Preoperative sagittal MRI T2 weighted image showing hyperintense signal of the spinal cord in C4-C5, above the level of CV fusion.

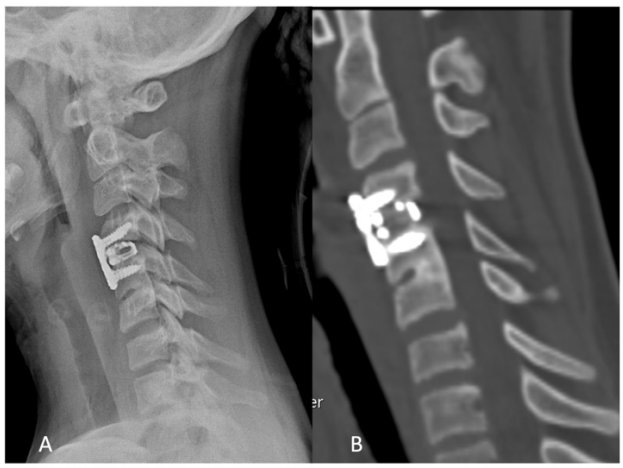

FIG 2: Postoperative imaging. A): Postoperative lateral X-Ray (A) and sagittal CT-scan (B) showing C4-C5 interbody fusion and anterior plating.

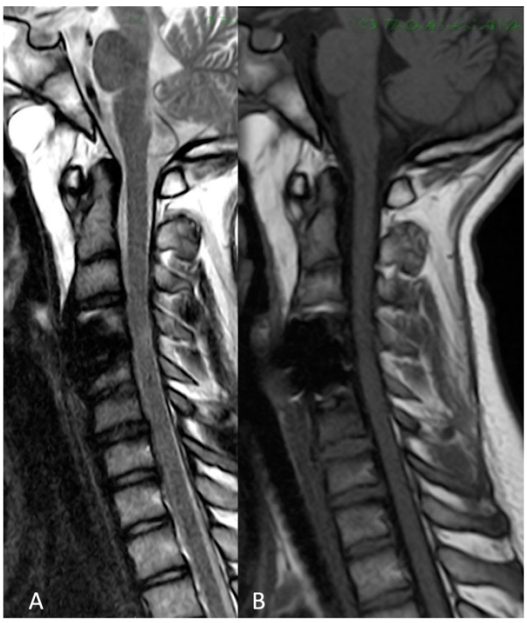

FIG 3: **Follow-up MRI** A-B) Six-months follow-up MRI in T1 (A) and T2 (B) weighted image showing the radiological improvement of preoperative sign of myelopathy.

LIST OF ABBREVIATIONS

3D	Threedimensional
AAO-HNS	American Academy Of Otolaryngology–Head And Neck Surgery
ABC/HRP	Avidincomplexed With Biotinylated Peroxidase
ACDF	Anterior Cervical Discectomy And Fusion
AICA	Anteroinferior Cerebellar Artery
ALIF	Anterior Lumbar Interbody Fusion
ALL	Anterior Longitudinal Ligament
AMA	American Medical Associate
ASD	Adult Spine Deformity
bFGF	Basic Fibroblast Growth Factor
BiCROSS	Conventional (Bilateral) Contralateral Routing Of Signals
BNI	Barrow Neurological Institute Pain Intensity Score
CAD/CAM	Computer-Aided Design/Computer-Aided Manufacturing
CHT	Chemotherapy
CI	Cochlear Implant
CISS	Constructive Interference In A Steady State
CLP	Cleft Lip And Palate
CNC	Consonant Nucleus Consonant
COX-2	Type 2 Cyclooxygenases
CP	Cranioplasty
CROSS	Conventional Contralateral Routing Of Signals
CSF	Cerebro Spinal Fluid
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTS	Carpal Tunnel Syndrome

CVA	Cervical Vertebrae Anomalies
cVEMPs	Cervical Vestibular Evoked Myogenic Potentials
CVS	Cystic Vestibular Schwannoma
DC	Decompressive Criotomy
DDD	Degenerative Disc Disease
DVP	Deep Venous Thrombosis
DWI	Diffusion-Weighted Images
ED	Emergency Department
EI	Epidural Hematoma
ENG	Electronystagmography
EV	Extracellular Vesicles
FC	Postoperative Fluid Collection
FIESTA	Fast Imaging Employing Steady State
FLAIR	Fluid Attenuated Inversion Recovery
FR	Prosthesis Fracture
GCS	Glasgow Coma Scale
GK	Gamma Knife
GK-SRS	Gamma Knife Stereotactic Radiosurgery
GKRS	Gamma Knife Radiosurgery
GM-CSF	Granulocyte-Macrophage Colony–Stimulating Factor
GNP	Glossopharyngeal Neuralgia
GR	Gardner–Robertson Hearing Scale
GSI	Spinal Cord Gunshot Injuries
GTR	Gross Total Resection
GW	Gunshot Wounds
H	Hydrocephalus
HA	Hearing Aids
HDRS17	Hamilton Depression Scale
HHI	Hearing Handicap Inventory
HIT	The Head Impulse Test
Hl	Hearing Loss
IAC	Internal Auditory Canal

ICH	International Conference Of Harmonization
ICHD	International Classification Of Headache Disorders
IF	Postoperative Infection
IHP	Inferior Hypogastric Plexus
IMSCTs	Intramedullary Spinal Cord Tumors
IR-FSPGR	Inversion Recovery-Prepared Fast Spoiled Gradient Echo
KFS	Klippel-Feil Syndrome
KPS	Karnofsky Performance Scale
LC	Local Control
LGKP	Leksell Gamma Knife1 Perfexion
LGP	Leksell Gamma Plan1
LINAC	Linear Accelerator
LL	Lumbar Lordosis
LLIF	Lateral Lumbar Interbody Fusion
LLL	Lower Lumbar Lordosis
LMWH	Low-Molecular-Weight Heparins
MEP	Motor Evoked Potential
MMs	Metastatic Meningiomas
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Scale
MVD	Microvascular Decompression
N/A	Not Available.
NF2	Neurofibromatosis Type 2
NRT	Neural Response Telemetry
NVC	Neurovascular Conflict
OAR	Organs At Risk
OD	Oswestry Disability Index
OS	Overall Survival
oVEMPs	Ocular Vestibular Evoked Myogenic Potentials
PAD	Deficiency Of The Posterior Arch
PCA	Ponto-Cerebellar Angle

PD	Prosthesis Displacement
PDS	Post Discectomy Syndrome
PEEK	Polyetheretherketone
PFS	Progression-Free Survival
PHA	Porous Hydroxyapatite
PI	Pelvic Incidence
PICA	Posterior-Inferior Cerebellar Artery
PMMA	Poli-Methyl-Methacrylate
PRT	Hermocoagulation
PT	Pelvic Tilt
PTA	Pure Tone Average
QoF	Quality Of Life
RE	Retrograde Ejaculation
REZ	Root Entry Zone
RLNP	Recurrent Laryngeal Nerve Palsy
RT	Radiotherapy
SCM	Sternocleidomastoid
SDS	Speech Discrimination Score
SE	Spin Echo
SEP	Somatosensorial
SL	Segmental Lordosis
SLIC	Cervical Spine Injury Classification System
SN	Sensorineural
SNHL	Sensori-Neural Hearing Loss
SRS	Stereotactic Radiosurgery
SRT	Speech Reception Threshold
SS	Sacral Slope
SSD	Single Side Deafness
SSD	Single-Sided Deafness
SSQ	Speech Spatial Qualities
STR	Sub Total Resection
SVS	Solid Vestibular Schwannoma
TBI	Traumatic Brain Injury
THI	Tinnitus Handicap Inventory
THI	Tinnitus Handicap Inventory

TLICS	Thoracolumbar Injury Classification And Severity Scale
TLIF	Transforaminal Lumbar Interbody Fusion
TN	Trigeminal Neuralgia
TNFa	Tumor Necrosis Factor Alpha
TSE	Turbo Spin Echo
TSP	Tumor Suppressor Protein
TV	Target Volume
UW	Unilateral Weakness
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
VEMPs	Vestibular Evoked Myogenic Potentials
VF	Vertebral Fusion
VHL	Von Hipple Lindau
VNG	Videonystagmography
VOR	Horizontal Vestibuloocular Reflex
VS - VSs	Vestibular Schwannomas
WHO	World Health Organization
WRS	Word Recognition Score

CONCLUSIONS

One of the main goals of Neuroscience is to understand how cognition, emotion and behavior can influence the personal perception of disability and thus functional outcomes.
As neurosurgery is very closely integrated with several aspect of neuroscience research, at the beginning of my PhD, I tried to define the main question I was hoping to answer:
"Can a modern less invasive approach improve functional outcome in selected neurosurgical diseases?"
Through my work as PhD student, I focused my attention on the influence of hearing loss on the long-term patients' quality of life after stereotactic radiosurgery with Gamma Knife, a treatment for vestibular schwannomas less invasive than surgical resection.
After more than 10 years from Gamma Knife tumor control is still maintained and hearing outcomes remained stable. These results underline the benefits of a less invasive approach even in the management of skull base lesions. Hearing deteriorations occur mainly within 3 years after Gamma Knife. However, hearing function continues to deteriorate beyond the first 1-3 years. Beyond the first 3 years, although marginally influenced by ageing, hearing deterioration is mainly influenced by the effect of radiation toxicity. After more than 10 years from Gamma Knife the personal perception of hearing disability is influenced by emotion and behavior components. The impact of single side deafness on quality of life can be tolerated in absence of audiological decline of the controlateral ear. Hearing loss resulting from bilateral vestibular schwannomas, as in type 2 Neurofibromatosis, may conversely have a devastating impact. When bilateral severe/profound hearing loss occurs, hearing rehabilitation is indicated to restore, support communication, and improve the quality of life.
At the same time, I started a new position as neurosurgeon in a spine unit. Approaching spinal degenerative disease and deformity, I understood how the impact on health-related quality of life in these patients can be compared with other chronic and severe conditions. I deepened my knowledge on minimally invasive approaches also in spinal diseases observing the results on functional outcomes.
The choice of a less invasive approaches results in earlier clinical benefit (faster recovery and return to work), lower blood loss and shorter surgical time.
Consequently, thanks to the collaboration between different specialties, at the end of my PhD, I appreciated how decisive minimally invasive treatments and interdisciplinary approaches are to improve all steps of patients health care, including rehabilitation.
A less invasive approach, that is not a synonym of less difficult approach, can really improve patients outcomes and quality of life in neurosurgical diseases.