„CAROL DAVILA" UNIVERSITY OF
MEDICINE AND PHARMACY, BUCHAREST
DOCTORAL SCHOOL
MEDICAL FIELD

DOCTORAL THESIS SUMMARY

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2022
BUCHAREST

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AGGRESSIVE MENINGIOMAS: A SPECIAL CATEGORY OF HISTOLOGICAL AND IMAGISTIC MENINGAL TUMORS THAT IMPOSE PARTICULAR THERAPEUTIC SOLUTIONS.

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SUMMARY

INTRODUCTION

Meningioma represents the most common benign brain tumor in the central nervous system. In the history of cerebral meningiomas, the earliest evidence of a probable meningioma belongs to a skull about 365,000 years old, which was discovered in Germany. A first documented mention appears in 1614 when Prof. Felix Plater of the University of Bern published the first case presentation mentioning this term. Later, in 1774, Antoine Louis (a famous French military surgeon) published the first treatise on meningiomas entitled "Sur le tumeurs fongueuses de la duremere". In the following period there are various changes in the nomenclature of this type of brain tumors, the most important being those made by Jean Cruveilhier and Hermann Lebert, who introduced the term "tumeurs cancereuses de la duremere".

However, it was not until after John Cleland in 1864 that the association between pacchion granules and meningeal tumors was established. Working in Glasgow, Cleland described two leptomeningeal tumors at autopsy and considered them "hairy arachnoid tumors", managing to separate the growths from the dura mater.

The last stage in the development of the nomenclature of "meningioma" is attributed to the American School of Neurosurgery. William W. Keen, considered by the vast majority of the medical world to be the first American "brain surgeon," after his postgraduate collaboration with European leaders (Guillame Duchenne, later Rudolf Wirchow) chose the term "endothelium" to describe these lesions. In the context in which Prof. Harvey Cushing was one of Dr. Keen's disciples, he systematized all the knowledge in the field in the Treatise entitled "Meningiomas" [1], a work that created the right scientific context for the modern study of meningiomas and laid the foundations for treatment. surgical, based on criteria used at the time of writing this doctoral dissertation.

The modern term meningioma was first used in 1922 by Prof. Harvey Cushing to describe a variety of tumors that occur in the neuroaxis. Charles Oberling later separated them into subtypes based on cell structure.

The first WHO classification of meningiomas appeared in 1979, comprising 7 subtypes, and the last of them, published in 2016, includes 16 subtypes.

The first documented surgical resection of a basic skull meningioma was performed in 1835 by Zanobi Pecchioli, a professor of surgery at the University of Siena.

In 1887, William W. Keen resected a convex meningioma in Philadelphia, the first successful brain tumor to be removed in the United States. This type of tumor accounts for about 1/3 of all central nervous system tumors, reaching up to 35,000 newly diagnosed cases / year in the United States. There is a high incidence of meningioma in Eastern Europe, especially after the 1986 Chernobyl nuclear disaster [5].

Among meningiomas, according to the WHO (World Health Organization) classification, 90% of them are considered benign (grade 1), about 7% are considered atypical (grade 2) and the remaining about 3% are anaplastic meningiomas (grade 3).

From a histopathological point of view, this category of brain tumors has a slow degree of growth and are considered non-invasive tumors

GENERAL PART

CHAPTER 1. GENERAL CHARACTERISTICS OF CEREBRAL MENINGIOMAS

1.1. Overview

Meningiomas are extra-axial, slow-growing tumors that start at the level of the dura mater [2]. From an imaging point of view, meningiomas are described as having a wide implantation base at the level of the dura, which can cause adjacent hyperostosis. 32% of incidentally discovered meningiomas do not increase in size in the next 3 years of follow-up. Meningiomas are considered to be surgically indicated:

- progressive growth, documented imagistically;

- symptoms associated with lesions that cannot be controlled by conservative treatment;

- changes in adjacent brain tissue on the T2 sequence

Most meningiomas are considered surgically cured if the lesion can be completely removed. They are most often located in the brainstem, convex or in the sphenoid bone and may have calcifications in the lesion. Histologically, the presence of psammomatous bodies is often identified.

Meningiomas are the most common intracranial tumors, accounting for approximately 36% of central nervous system tumors. These are benign lesions that usually show a slow, non-infiltrative growth. About 10% have malignant histological features or have a rapid growth such as hemangiopericytoma, which can be confused with a meningioma. Meningiomas are the starting point for meningothelial cells in the arachnoid. In 8% of cases associated with neurofibromatosis, meningiomas may be multiple [3]. Meningiomas with a diffuse tumor layer (plaque meningiomas) can sometimes be described. Ectopic meningiomas may have as a starting point the bones of the neurocranium (primary intraosseous meningiomas) and others may evolve from the subcutaneous tissues, without cranial insertion [4]. Most of them are asymptomatic.

The risk factors for meningiomas are not well known. The only risk factor shown is ionizing radiation (usually with therapeutic doses of radiation), with a higher risk of childhood exposure. There appears to be a genetic susceptibility to developing XRT-induced meningiomas. The association of meningiomas with genetic syndromes such as neurofibromatosis type I or II is also recognized.

3% of the autopsies of patients over 60 years of age reveal the presence of meningioma [5]. Meningiomas represent 14.3-19% of primary intracranial neoplasms [6]. The peak of the incidence is 45 years old. The average age at which meningiomas are diagnosed is 65 years, the risk increasing in direct proportion to age. Women: 1.8: 1 men. Only 1.5% of meningiomas occur in children aged 10 to 20 years [7] and 19-24% of meningiomas in children occur in the context of type I neurofibromatosis.

1.2. Topography of meningiomas

The most common locations are shown in Table III.1. Other locations include: cerebellopontine angle, clivus, planum sphenoidale and foramen magnum. About 70% of meningiomas are located along the falx cerebri, at the level of the sphenoid bone or the convexities. Meningiomas in pediatric patients are rare and 28% are present intraventricularly or in the posterior fossa.

Sphenoid wing meningiomas:

1. Located at the lateral level of the sphenoid wing (pterional): the behavior and treatment are similar to those of convex meningiomas

2. Located in the middle third (alare)

3. Medial (clinoidal): tend to compress the internal carotid artery as well as the cranial nerves in the region of the superior oribital fissure or the optic nerve. The brainstem can be compressed. In most cases, total resection is not possible.

Parasagittal meningiomas:

More than half of these lesions invade the upper sagittal sinus. They are grouped based on the location at the level of the sinus as follows:

1. anterior (ethmoidal blade-coronal suture): 44%. Associated with mental status disorders.
2. middle (coronal suture-lambdoid suture): 33%. Associated with Jaksonian crises and progressive monoplegia.
3. posterior (lambdoid suture - torcular herophili): 23%. Associated with visual symptoms or epileptic seizures or mental status disorders.

Parasagittal meningiomas can originate in the motor area and the initial manifestation is "foot drop" [8].

Olfactory meningiomas

The symptoms caused by olfactory duct meningiomas may be represented by:

1. Foster Kennedy syndrome: anosmia, ipsilateral optic nerve atrophy and contralateral papillary edema
2. mental status disorders: apathy, abulia
3. urinary incontinence
4. visual disturbances
5. memory disorders caused by compression of the fornix
6. epileptic seizures

Morbidity, mortality and total ablation difficulty increase considerably in the case of formations larger than 3 cm.

Preoperative angiography may be helpful in locating the relationship between the cerebral arteries and the tumor. 70-80% of olfactory duct meningiomas are vascularized from the anterior ethmoid artery, which is usually not embolized due to the risk of blindness.

Meningiomas located in the planum sphenoidale

The starting point is the sphenoid bone, anterior to the chiasmatic groove.

Tuberculum sellae meningiomas

The origin of these tumors is about 2 cm posterior to the olfactory duct meningiomas. Tuberculum sellae is a bony excavation between the chiasmatic ditch and the Turkish saddle. By definition, the anterior edge of the chiasmatic groove (limbus sphenoidale) is the boundary between the anterior and middle fossa [9].

Tuberculum sellae tumors are characterized by visual disturbances. They can be confused with pituitary microadenomas when they grow posteriorly.

Foramen magnum meningiomas

The symptoms of these tumors can be very wide and often do not suggest the presence of a tumor at this level. 31% have as a starting point the anterior margin of the foramen magnum, 56% have meningiomas as a starting point the anterior edge of the foramen magnum and 13% have the posterior margin. Most are intradural, but can also be extradural or mixed [10].

1.3. Pathological classification and risk of recurrence

Given the fact that there are multiple pathological classification systems, four critical histopathological variants have been detected that affect the recurrence rate:

1. grade
2. histological subtype
3. proliferation index
4. brain invasion

1. meningiomas with a low risk of both recurrence and / or aggressive growth

a. meningothelial or meningothelioma, syncytial AKA: most common. Polygonal cell layers. Some use the term angiomatous for the type of meningothelioma with tight blood vessels;
b. fibrous or fibroblastic: cells separated by the conjunctival stroma. The consistency is rougher than meningothelioma or transitional;
c. transient: intermediate between meningothelioma and fibrous. The cells tend to be spindle-shaped, but there are areas of typical meningothelioma cells. Swirls, some of which are calcified (psammomatous bodies);
d. psammomatosis: calcified meningothelial vortices;
e. angiomatous;
f. microcystic: AKA "wet" or vacuolated meningioma. The characteristic dilated extracellular spaces are usually empty, but occasionally contain substances that have a positive effect on PAS (glycoproteins) or fats [11]. Cysts may join and form coarsely or radiologically visible cysts that may resemble astrocytomas;
g. secretory;
h. rich in lymphoplasmocytes;
i. metaplastic meningioma;

2. meningiomas with a higher risk of recurrence and / or aggressive growth (mainly WHO grade II and III). It includes:

a. atypical meningioma: increased mitotic activity (mitotic figure 1-2 / strong field), increased cellularity, focal areas of necrosis, giant cells. Cell pleomorphism is not uncommon, but it is not significant in itself. The increase in atypicality seems to correlate with the increasing aggression.
b. rhabdoid meningiomas: they usually have malignant features and behave aggressively. Behavior in the absence of malignant traits is undetermined.
c. malignant meningiomas: anaplastic, papillary or sarcomatous AKA. Characterized by frequent mitotic divisions, cortical invasion, rapid recurrence even after total apparent removal, and rarely metastases. Frequent mitotic divisions ($\geq$ 4 mitoses per high power field) or the presence of papillary features are strong predictors of malignancy. It may be more common in younger patients.

d. meningiomas with high proliferation index.

Due to the variation between institutions and observers, it is recommended as proliferation indicators (eg Ki-67 or MIB-1) [13] should not be used as the sole discriminant for classification.

However, these indices correlate with the prognosis. The addition of "high proliferative activity" is suggestive of high index tumors.

Brain invasion

The presence of brain invasion increases the likelihood of recurrence at levels similar to atypical (not anaplastic) meningiomas [14], but is not an indicator of the degree of malignancy. Invasion of the brain in atypical meningiomas does not dictate malignant behavior. The addition of the phrase "with brain invasion" indicates a higher degree of recurrence.

Metastases

Very rarely a meningioma can metastasize outside the CNS. Most of these are angioblastic or malignant. The lungs, liver, lymph nodes and heart are the most common places.

1.4. Differential diagnosis / diagnostic considerations of meningioma

1. Multiple meningiomas: suggest neurofibromatosis 2 (NF2)
2. pleomorphic xanthoastrocytoma (PXA): may mimic meningiomas, as they tend to be located peripherally and may have a dural pedicle
3. gliosarcomas, especially those that are predominantly carcomatos
4. Rosai-Dorfman disease: especially if extracranial lesions are also identified.

A connective tissue disorder with sinus histiocytosis and painless massive lymphadenopathy (most have cervical lymphadenopathy). Usually in young adults. Isolated intracranial damage is rare. MRI: Dural load with signal characteristics similar to meningioma, may have dural pedicle. The most common intracranial localizations: cerebral convexity, parasagittal, suprasellar, cavernous sinus. Pathology: dense fibrocollagenous connective tissue with spindle-shaped cells and lymphocytic infiltrates. Histiocytic proliferation without malignancy. Foamy histiocytes are characteristic. Surgery and immunosuppressive therapy are not effective. Low dose XRT may be the best option.

1.5. Symptomatology of meningiomas

Symptoms depend on the location of the tumor and some specific locations are associated with well-described symptom complexes. Supratentorial meningiomas can cause seizures due to irritation of the cerebral cortex.

Meningiomas are the most common primary intracranial tumors and most remain asymptomatic [14]. Routine use of CT and MRI for many indications as a result of the incidental detection of meningiomas (asymptomatic). In a population-based study (the study population consisted of middle-class Caucasians and the result may not be generalizable to other groups), 23 accidental meningiomas were observed in 0.9% of MRI. In another series, 32% of the primary brain tumors observed were meningiomas, and 39% were asymptomatic [15]. Of the 63 cases followed for more than 1 year with non-surgical management, 68% did not show an increase in size, while 32% showed a slow progressive increase. Asymptomatic meningiomas with calcifications observed on CT and / or hypointensity on T2WI NMR appeared to have a lower growth rate.

There is not enough data for a standardized management guide. One suggestion is to obtain a continuation of the imaging study 3-4 months after the initial investigation to rule out rapid progression and then repeat annually for 2-3 years. The appearance of the symptoms determines the performance of a study at that time.

CHAPTER 2. TREATMENT OF CEREBRAL MENINGIOMAS

2.1. Surgical treatment

Treatment is indicated for lesions that produce symptoms but cannot be controlled satisfactorily from a medical point of view or for those that show a significant continuous increase in serial imaging studies. At the time of surgery, the rate of perioperative morbidity was statistically significantly higher in patients> 70 years of age (23%) than in patients <70 (3.5%).

The treatment of choice for symptomatic meningiomas is surgical. Incidental meningiomas without edema or those that cause epileptic seizures can be treated conservatively with drug treatment. Radiation therapy is considered in patients who cannot undergo surgery, for deeply localized meningiomas, for multiple recurrences as well as for malignant or atypical meningiomas, regardless of the degree of resection or after the first recurrence.

These tumors are very bloody [34]. Preoperative embolization and blood transfusions can be very helpful for these lesions. General principles of meningioma surgery:

1. early interruption of the vascular source;
2. internal decompression (using ultrasonic vacuum cleaner and cauterization handles);
3. dissection of the tumor capsule by cutting and vascular coagulation of the arachnoid inserts with minimal retraction of the brain;
4. excision of the bone and dural insertion when possible.

Positioning in the operating room

The head should be raised approximately 30 degrees above the right atrium [35].

For upper sagittal sinus meningiomas (SSS):

- Anterior third of the SSS: supine position semi-sitting

- Middle third of the SSS: lying side down containing the tumor down, neck bent 45 degrees anteriorly and shoulders raised

- Posterior third of the SSS: ventral decubitus.

Meningiomas of the sphenoid wing, parasagittal or tail of the brain

Once the tumor is exposed, a partial internal defragmentation is performed. The attachment point (to the falx or sphenoid bone) is then removed using the bipolar forceps to divide the feeding vessels. Then, the main part of the tumor can be separated from the brain, the tumor being avascular once the vascular pedicle has been removed.

Parasagittal and falx meningiomas

The lower part of the tumor may adhere to the branches of the anterior cerebral artery. Middle or posterior fossa tumors are exposed using a horseshoe-shaped incision based on the direction of the major scalp supply vessels. The patient may be placed in a lateral or sitting position. Can be used with Doppler monitoring for air embolism. Anterior grave tumors are treated using a bicoronal skin incision with the patient lying on his back. For midline tumors, drill holes are placed to prevent SSS damage.

Because these tumors are often fragmented from the inside, the removal tends to be more bloody than in the case of meningiomas that can be removed in one piece. The ability to embolize these preoperative tumors is somewhat limited, but may be an adjunct. Technique: Incise the tumor leaving a thin layer on the hard. Then the relatively avascular part that compresses the brain is removed. It is then incised through the dura near the tumor. It tends to be bloody, but once the bleeding is controlled on both sides of the dura, you may begin to excise the dura around the tumor (it may be necessary to leave a cuff on the SSS if it is involved).

Sphenoid wing meningiomas

A pterional craniotomy is used. The neck is extended to allow gravity to retract the brain from the base of the skull.

Lateral sphenoid wing meningiomas: The approach to these tumors is often similar to convex meningiomas. The size of the incision and the bony flap should be large enough to encompass the tumor.

Medial sphenoid wing meningiomas: a lumbar drain is used. The head is positioned at 30 degrees vertically. An FTOZ approach can provide additional exposure.

The edges of the silvial fissure are widely retracted. The internal carotid artery and the middle carotid artery are often covered by the tumor. To locate the ICA, identify the MCA branches and follow them proximally to the tumor. The optic nerve is the easiest to identify when entering the optic canal. Avoid excessive retraction of optical structures. The deep part of the tumor often has many small vessels in the ICA (which makes this part very bloody) and can also invade the lateral wall of the cavernous sinus (which creates a risk of cranial nerve deficiencies with the attempt to remove). Therefore, the recommendation is to subtotally excise the tumor lesion and use radiosurgery to treat the remaining tumor portion.

Olfactory groove meningiomas

It is approached by a bifrontal craniotomy (keeping the periosteum to cover the frontal sinus and the floor of the anterior fossa at the end of the operation) [36]. Small tumors can be treated by unilateral craniotomy on the side with the largest tumor. For large tumors, lumbar puncture by lumbar puncture will help relax the brain and rotate the head to 20 ° to one side to facilitate dissection of the anterior cerebral arteries and optic nerve while maintaining visualization of the tumor. The neck is slightly extended. The dura is open inferiorly, and the superior sagittal sinus is ligated. Amputation of the front pole should be done, if necessary, to avoid excessive retraction.

The vascular supply arteries come through the floor of the anterior fossa on the midline. Initially, the anterior tumor capsule is opened and the tumor is fragmented from the inside, heading to the floor of the anterior fossa to interrupt the blood supply [37]. The posterior capsule of the tumor is carefully dissected, as this portion of the tumor may comprise branches of the anterior cerebral artery and / or the optic nerve and chiasm. A large tumor with an suprasellar extension usually displaces the inferior optic nerve and chiasm. If necessary, the fronto-polar branch and other small branches can be sacrificed without repercussions. The periosteum is placed on the floor of the anterior fossa. To hold it in place, you can try to suture the adjacent dura with a few sutures, alternatively a small titanium plate (eg "Dogbone") can be placed over the flap and the screws are placed in the floor bone of the anterior fossa (both methods are difficult) . Postoperative risks include CSF leakage through the ethmoid sinuses.

Meningiomas tuberculum sellae

These tumors can usually displace the optic nerves, posterior and lateral. Occasionally, the nerves are completely covered by the tumor.

Cerebellopontin angle meningiomas

They usually appear in the meninges that cover the petrosal bone. It can be divided into those that appear before and those that appear after the IAC.

Foramen Magnum meningiomas

Tumors that appear from the posterior or posterolateral margin of the foramen magnum (FM) are relatively easily removed. Anterior and lateral FM tumors can be operated by the posterolateral approach, and a transcondylar approach can be used alternatively for anterior tumors.

With meningiomas below the vertebral artery (AV), the lower cranial nerves are displaced superiorly by the AV. However, when the tumor is superior to AV, the position of the inferior cranial nerves cannot be anticipated. Large tumors can adhere or cover the neurovascular structures, and these should be fragmented from the inside and then dissected.

Posterior suboccipital approach: used for meningiomas that appear from the posterior edge of the FM or slightly posterolateral. The surgeon should be vigilant to observe the PICA and the vertebral arteries, which may be entangled.

“Wait and See” Strategy

For asymptomatic small tumors (diameter <3 cm), the periodic imaging follow-up strategy can be adopted. The same attitude can be applied to elderly patients or those with major comorbidities (where the surgical risk is maximum). The European Neuro-Oncology Association (EANO) suggests contrast-enhanced meningiomas for small or small meningiomas 6 months after diagnosis, and if tumor size and symptoms remain the same at the time of diagnosis, an annual evaluation will be used. However, if tumor growth is found during follow-up or localization-specific symptoms, active management is recommended [16], [17], [18], [19], [20].

2.2. Radiotherapy (XRT)

Generally considered ineffective as a primary treatment. Many prefer not to use XRT for "benign" lesions. The effectiveness of XRT in preventing recurrence is controversial. Some surgeons reserve XRT for malignant (invasive), vascular, rapid ("aggressive") or unresectable meningiomas. For recurrent atypical or anaplastic meningioma with postoperative residual disease, XRT with 55-60 Gy is recommended.

Radiation therapy as a management of meningiomas is suitable for the following categories of patients: patients diagnosed with WHO grade II or III meningiomas, patients with subtotal tumor resection degree, patients who missed surgery for various reasons, tumor recurrence or patients without the possibility of undergoing surgery. The purpose of radiotherapy is to reduce the ability of tumor proliferation and to control the process of dimensional progression [21].

Fractional radiotherapy increases the tolerable dose for important intracranial structures (such as the optic tract) and minimizes the adverse effects of radiotherapy. Conventional radiotherapy for meningiomas with subtotal surgical resection or recurrences has been shown to improve control of dimensional progression. Unconventional fractional radiotherapy does not yet have a proven effect on the management of meningiomas, and includes Hypo and Hyper Fractional radiotherapy [22].

Simultaneously with technological development, radiotherapy is more precise and, more importantly, individualized for each case. Precision radiotherapy technology includes 3D-CRT radiotherapy, intensity-controlled radiotherapy (IMRT), imaging-guided radiotherapy, and real-time dynamic radiotherapy. Stereotactic radiotherapy (SRT) is an improvement over conventional radiation therapy. This technology can irradiate a specific target with a high dose of radiation in a single therapy session, with minimal irradiation outside the "target" and without damaging adjacent brain tissue. Fractional stereotactic radiotherapy (FSRT) may reduce the dose of peripheral brain tissue exposure to tumor lesion, with results similar to conventional stereotactic therapy. Stereotactic radiosurgery (SRS) was developed by combining radiotherapy with stereotaxy, being suitable for meningiomas with a maximum diameter <3 cm and located at> 3 mm of radiosensitive brain structures (eg optic nerve). Improving this technique currently allows for both repeated fractional therapy and fractional radiosurgery for large tumor lesions.

The low recurrence rate for WHO grade I meningiomas after total resection is relatively low, so the vast majority of neurosurgeons do not recommend postoperative adjuvant radiotherapy. We must keep in mind, however, that the recurrence rate after subtotal surgical resections is quite high, which leads to the recommendation of adjuvant radiotherapy in these cases. Grade II and III meningiomas can be considered invasive. Some studies mention the recurrence rate between 30 and 80% at 5 years postoperatively, so radiotherapy is considered in these situations immediately after surgery regardless of the degree of tumor resection. Radiotherapy for WHO grade II meningiomas remains controversial, with several clinical trials currently underway to confirm the role of radiation therapy for WHO grade II and III meningiomas.

2.3. Chemotherapy

Chemotherapy drug therapy can be performed only after the surgical or radiotherapy options have been exhausted, more precisely in the case of meningiomas with recurrence or tumor progression. There is a wide variety of chemotherapeutics as well as molecular treatments for the management of malignant meningiomas such as alkylating agents, tyrosine kinase inhibitors, endocrine drugs and interferon. Although many treatments have been shown to be effective in preclinical studies and some clinical applications, there is no drug of choice to be identified as a chemotherapeutic agent for the treatment of meningiomas.

Hydroxyurea (HU) is a reductase inhibitory ribonucleic acid that induces meningeal cell apoptosis by preventing activation of the S phase of the cell cycle. HU has been used as adjunctive therapy for meningiomas with subtotal resection or recurrences. Weston and colleagues concluded that although HU may prevent recurrence in some cases, it does not reduce tumor volume and has multiple side effects [23].

Chamberlain published a retrospective case study of 35 patients with high-grade meningiomas who relapsed after surgery and radiation therapy (22 WHO grade II cases and 13 WHO grade III cases) who received HU, with an increased prognosis of survival only in 3% of cases and a follow-up of only 2 months [24].

Temozolomide (TMZ), an alkylating agent, was unsuccessful in recurrent meningiomas.

Chamberlain and colleagues treated 16 patients with refractory meningiomas. The time to tumor progression was 2.5-5 months, and the average survival period ranged from 4 to 9 months [25].

Irinotecan, a topoisomerase I inhibitor, in clinical trials shows that it may be an inhibitor of tumor meningeal cell growth, which is refuted by phase II trials.

Recombinant interferon α-2b has also been reported to be effective in patients with malignant meningiomas.

Genetic studies have confirmed the importance of genetic mutations such as NF2, TRAF7, KLF4, AKT1, SMI, PI3KCA and POLR2A for the appearance and development of meningiomas. Between 50 and 60% of meningioma patients have mutations characteristic of type 2 neurofibromatosis. Genetic mutations determine possible mitogenic developmental pathways, including mitogen-activated protein kinase (MAPK), phosphoinositide 3-linase (AKT), and extracellular signal control kinase (ERK) [26].

Epidermal growth factor (EGFR) is found in 60% of meningiomas. Activation of the epidermal growth factor (EGF) receptor or transforming growth factor (TGF-α) receptor may promote in vitro proliferation of meningeal cells. In a study of 25 patients with recurrent meningiomas treated with EGFR, Gefitinib and Erlotinib inhibitors, although treatment is well tolerated, neither gefitinib nor erlotinib has obvious activity on recurrent meningiomas.

VEGF was found to be positive in 84% of meningiomas and the VEGF receptor (VEGFR) was present in 67% of meningiomas. The level of VEGF and VEGFR expression in meningiomas increases with increasing tumor size. Inhibition of VEGF and VEGFR may have a significant anti-tumor effect. Studies have shown that bevacizumab, a VEGF inhibitor, has clinical benefits in meningiomas without a response to surgery or radiation therapy and may improve the survival rate of patients [27]. However, due to the lack of strong clinical evidence for improvement in survival given the associated rate of toxicity, treatment of meningiomas with bevacizumab should be carefully evaluated. Vatalanib can effectively inhibit VEGFR and PDGFR and has antitumor activity in grade II and grade III meningiomas.

mTORC1 can attenuate RTK signals through PI3K and Akt thus forming a negative feedback loop. Inhibitors of the mTOR pathway, such as Temsirolimus and Everolimus, have been shown to be effective in preventing the progression of meningiomas [28]. In addition, in vitro studies have shown that retinol-like compounds, such as Fenretinide, can bind to the retinoic acid receptor (RAR) to induce apoptosis in meningioma cells [86]. Clinical trials with Vismodegib and Afureserib, specifically drugs for meningiomas with mutations in SMO and AKT1, are ongoing.

Studies have shown that there is a strong relationship between sex hormones and meningiomas. Estrogen receptor (ER) is expressed in low levels in approximately 10% of patients diagnosed with meningiomas, while progesterone (PR) and androgen receptor are expressed in 70% of patients with meningiomas. Due to the low level of RE expression, the treatment of the RE antagonist, namely tamoxifen, did not show any effective results. The results of the antiprogestin / mifepristone study are also uncertain. Somatostatin (SST) plays an important role in regulating the proliferation of normal cells and tumor cells. Long-term SST analogues are now recommended for the systemic treatment of unresectable or radiorefractive recurrences. A recent study looked at the effectiveness of the chemotherapeutics Everolim and Octreotid in the treatment of recurrences with survival rates at 6 and 12 months at 90 and 75%, respectively. The study suggests that the use of the combination of everolimus and octreotide should be considered as an effective chemotherapeutic treatment for meningiomas [29].

2.4. Gene therapy

Gene therapy is the introduction of genetic material (DNA or RNA) into human cells to correct or compensate for defects in genes and abnormalities in order to achieve therapeutic goals. The researchers found that adenovirus and herpes virus can be effectively transmitted to meningioma cells. Herpes simplex virus is the first effective oncolytic virus in the treatment of meningiomas [30]. Due to the short duration of the therapeutic effect and the uncontrollable insertion mutation, only a few preclinical studies have been reported, which also provides a new direction for gene therapy for meningiomas.

CHAPTER 3. HYPOTHESIS AND OBJECTIVES

The study of cerebral meningiomas is an ongoing challenge. Recent discoveries in the field of genetics of this category of brain tumors, the complexity of the surgical procedure, as well as the combination of radio and chemotherapy, taking into account a signal to be taken into account in the management of meningiomas. In these conditions, we decided to deepen the study of meningiomas in the Neurosurgery Service IV.

Thus, this thesis wants to introduce in the specialized nomenclature a new phrase associated with meningiomas (regardless of histopathological subtype) which, based on the collaboration between neurosurgeons, histopathologists and radiographers, to determine the degree of aggression of this brain tumor pathology, the prognosis in depending on the therapeutic options chosen and increase the success of surgery.

Studying the eloquent international databases (Pubmed, Journal of Neurosurgery) for the specialty of neurosurgery, we find very few specialized articles (usually case presentations) that associate the 2 words from the proposed nomenclature (aggressive meningioma).

In 1986, Schmidt *et al* [31] first used the term aggressive meningioma to describe the aggressiveness of a meningioma by extending it to the jugular vein, a rare situation that led to a cautious surgical approach, performing a biopsy prior to total resection. , and the neurological status of the patient was much worse compared to that of hospitalization.

In 1999, Nasaku *et al* [32] conducted a study of the likelihood of local recurrence in patients treated surgically for meningeal tumors in a group of 101 patients treated in Ohtsu, Japan. The study found a recurrence rate of 15%, the only predictive factor found being the macroscopic appearance of the tumor, without other statistically significant criteria (macroscopic appearance polylobulated or "mushroom").

In 2007, Bikmaz *et al* [33] published a study of a group of 17 patients with sphenoid wing meningiomas with secondary bone invasion, in whom the authors performed "gross total resection" in 82% of cases and had a recurrence rate of only 7%.

In their article published in 2015, Buttrick et al [34] noticed the increase of malignancy and recurrence of meningiomas and a decreased life expectancy at 5 years for Grade II and III WHO scale meningiomas.

In 2016, Hou *et al* [35] used the term “Invasive Meningioma” to describe the histopathological, imaging, and intraoperative features of these lesions that invade neighboring structures. In contrast to this doctoral thesis, the authors of this study considered the invasion of a single adjacent anatomical element to determine the degree of invasion, on a group of 59 patients treated over a period of 3 years.

In 2018, Hess *et al* [36] conducted a study of 108 children with meningeal tumor pathology with invasion of the brain parenchyma, analyzing the risk of secondary seizures. Following the analysis performed on the study group, it was concluded that the risk of preoperative seizures is directly proportional to the degree of parenchymal invasion, which decreases dramatically postoperatively.

As was mentioned before, there is a small amount of specialized articles on the topic proposed in this doctoral thesis, only in one case there are references similar to the working hypothesis of this thesis. Furthermore, the number of patients included in our study group is significantly larger than in the articles mentioned before, which provides significant statistical results, as will be seen in the following chapters. From the criteria taken into consideration point of view, we can highlight the conclusive aggression / invasion criteria, both from an imaging, histological and surgical point of view.

Also, with this doctoral thesis, we tried to change the paradigm of case analysis in the case of dural brain tumor pathology, in order to mentain a close collaboration with fellow histopathologists and radiologists in creating a multidisciplinary team, to have a definitive diagnosis, to choose the best medical treatment plan and adjuvant when appropriate.

CHAPTER 4. METHODOLOGY

The personal interest related to brain tumors, especially the category of intracranial meningiomas, was a decisive factor in choosing the topic of the doctoral thesis, managing to identify a particular aspect of meningioma pathology underdeveloped and mentioned in the literature.

Thus, using clinical, imaging and histopathological criteria, we managed to develop a scale for the particular analysis of meningiomas and, possibly, for the prognosis of their evolutionary aggression.

Inclusion criterias in the study were represented by (1) parenchymal invasion, (2) invasion of large blood vessels, (3) osteolysis without involvement of the external skull and (4) complete osteolysis with secondary aesthetic defect, were carefully selected using colleagues from the staff of the Radio-Imaging Laboratory and the Histopathology Service, emphasizing the importance of interdisciplinary collaboration for the benefit of patients. To the same extent, with their help the above criteria have undergone adjustments compared to their original form. It should be noted that only cases that met at least 2 of the 4 criteria mentioned above were included in the study.

The exclusion criteria from the study were: (1) the association of aggressive meningiomas with other genetic syndromes (neurofibromatosis, meningiomatosis), (2) incomplete statistics, (3) minor patients and (4) lack of patient consent.

The study quantifies the following parameters: (1) gender distribution, (2) age grouping, (3) patient background (rural/urban), (4) scholarship status, (5) length of hospitalization, (6) comorbidities, (7) symptomatology at admission, (8) radiological investigations, (9) tumor location, (10) tumor size, (11) radio-imaging features, (12) treatment methods, (13) resection degree, (14) surgical attitude, (15) postoperative complications, (16) histopathological features, (17) invasion of adjacent anatomical structures, (18) Karnofsky score, (19) postoperative follow-up.

Between 01.01.2015 and 31.12.2019, within the Neurosurgery IV Service of the Emergency Clinical Hospital "Bagdasar-Arseni" were treated 3149 brain tumors of which 1921 benign brain tumors (61%), in relative accordance with the specialized data.

Of the benign tumors (1921 cases), 1521 meningiomas were identified, representing 79.1% of all benign brain tumors and 48.3% of all brain tumors treated in our Service, a high percentage compared to 36.4% of all intracranial tumors described in the literature.

Out of the 1521 meningeal brain tumors, a number of 290 cases were included in the study, which represents 19.06% of the total meningiomas treated, cases with at least 2 inclusion criteria.

The criteria for inclusion in the study were obtained from the individual study of the observation sheets from the archives of the Neurosurgery Service IV within the Emergency Clinical Hospital "Bagdasar-Arseni", as well as the use of “Hippocrates” and “FOBS” electronic observation sheets programs (accepted by the Romanian Ministry of Health).

Also, the results obtained in this study are surprising, considering the specialized literature. The very high percentage of cerebral meningiomas included in the study (approximately 1/5 of all meningiomas treated either conservatively or surgically) is in the general note, observed in the specialized works of recent years, of revolutionizing/modifying the "general data" regarding cerebral meningiomas.

Microsoft Excel (for graphs, tables, and simple statistical analysis) and SpSS (for advanced statistical analysis) were used for the results obtained.

CHAPTER 5. OUTCOMES

5.1. General outcomes

In our study, out of the 290 patients selected, 182 were female and 108 male, respectively, in a percentage of 62.75% women and 37.25% men, with a ratio of approximately 1.7 / 1.

From the point of view of distribution by age groups, 2 patients were between the 20-30 years, 19 patients were between the 30-40 years, 47 patients were between the 40-50 years, 145 patients were between the 50-60 years, 66 patients were between the 60-70 years, 8 patients were between 70-80 years and 3 patients were between the 80s and 90s. The median age was 56.9 years, with a minimum of 24 years and a maximum of 87 years.

Analyzing the origin of patients, 167 (57.5%) patients come from urban areas and 123 (42.5%) patients from rural areas. The scholarship of the study group reveals 71 patients with higher education diplomas, 112 patients with high school diploma, 58 patients with secondary school certificate and 49 patients without any type of completed scholarship.

5.2. Outcomes regarding the population with meningeal brain tumors

In terms of length of hospital stay (number of days) we have the following results: 101 patients with hospitalization less than 10 days, 96 patients with hospitalization between 10 and 20 days, 62 patients with a hospitalization between 20 and 30 days and 31 patients with a hospitalization of more than 30 days.

Comorbidities were present in most of the cases, so we mention the following: 145 patients with associated cardiac pathology, 99 patients with associated metabolic diseases, obesity present in 63 cases, patients with neurological disorders in 84 of cases, and patients with associated comorbidities other than those mentioned above in 141 cases.

In terms of symptoms, 246 of the patients had various manifestations of Intracranial Hypertension Syndrome, 201 presented various Lobe Syndromes, 19 presented seiszures, 27 patients with Cranial Nerve Syndromes and 77 with neurological other manifestations.

246 of the patients had before or during the hospitalization a Brain Computed Tomography, the whole group of 290 of them performed a cerebral Magnetic Resonance Imaging, and a number of 115 patients benefited during the hospitalization of a classic Cerebral Angiography.

Based on the radio-imaging investigations performed, the following locations were established: 186 patients with supratentorial meningiomas, 36 with infratentorial localization, 51 with localization at the level of the skull base, and 17 at the level of the tentorium.

The supratentorial localizations were subdivided into 53 cases with frontal localization, 28 with temporal localization, 41 with parietal localization, 19 with occipital localization, and 45 cases with mixed localization.

Tumor size were established based on imaging measurements as it follows: 3 cases with sizes between 10 - 20 mm, 9 cases with sizes between 20 - 30 mm, 140 cases with sizes between 30 - 40 mm, 89 cases with sizes between 40 - 50 mm, 44 cases with sizes between 50 - 60 mm, 16 cases with sizes between 60 - 70 mm and 7 cases with sizes between 70 - 80 mm and 2 cases with sizes between 80 - 90 mm (the tumor diameter is maintained in all cases above mentioned).

From an imaging point of view, there were 184 cases of ventricular compression, 135 cases of midline displacement and 57 cases of hydrocephalus. Thus, out of the 290 cases, 281 underwent surgery and 9 cases were treated conservatively / refused surgery.

Using the Simpson scale of resection in meningiomas we have the following results: 221 patients with Simpson 1, 50 patients with Simpson 2, 11 patients with Simpson 3, 8 patients with Simpson 4 and 1 patient with Simpson 5.

In 45 cases out of 290, it was necessary to perform decompressive craniectomy, and in the previously mentioned cases only 31 patients returned for cranioplasty, 11 patients being lost from the record by not following the control protocol.

As post-operative complications we mention the following: 22 postoperative arachnoid cysts, 41 CSF fistulas, 19 cases of intraparenchymal hematomas at the level of the tumor bed, 7 wound / flap infections, 23 cases of post-resection epilepsy, 17 cases of hydrocephalus and 36 cases of neurological worsening. Out of the 290 cases, 11 deaths were recorderd.

5.3. Outcomes related to the histopathological criteria regarding the occurrence of recurrences and tumor progression

Regarding histopathological features we have the following statistical data: 69 cases of meningiomatous meningiomas, 52 cases of fibrous meningiomas, 13 cases of transitional meningiomas, 11 cases of psamomatous meningiomas, 41 cases of angiomatous meningiomas, 16 cases of microcystic meningiomas, 17 cases of secretory meningiomas, 5 cases of metaplastic meningiomas, 38 cases of atypical meningiomas, 6 cases of cordoid meningiomas, 11 cases of anaplastic meningiomas, 7 cases of rhabdoid meningiomas and 4 cases of papillary meningiomas.

Of the 290 cases, 29 had tumor recurrence (6 transitional mengiomas and 23 atypical meningiomas), and another 19 had tumor progression to anaplastic meningiomas (4 transitional meningiomas and 15 atypical meningiomas).

5.4. Outcomes regarding the inclusion criteria in the study and the Karnofsky score

Thus, taking into account the inclusion criteria in the study, we have 225 cases with parenchymal invasion, 204 cases with vascular invasion, 139 cases with bone invasion and 61 cases with major aesthetic defects. All 290 cases met at least 2 inclusion criteria in the study, 216 presented 3 inclusion criteria in the study and 61 cases met all 4 inclusion criteria.

Achieving the Karnofski score in the study group indicated the following results: 89 patients with a score of 100, 97 patients with a score of 90, 12 patients with a score of 80, 15 patients with a score of 70, 11 patients with a score of 60, 13 patients with a score of 50, 6 patients with a score of 40, 20 patients with a score of 30, 7 patients with a score of 20, 9 patients with a score of 10 and 11 patients with a score of 0.

CHAPTER 6. DISCUSSIONS

The personal interest related to brain tumors, especially the category of intracranial meningiomas, was a decisive factor in choosing the topic of the doctoral thesis, managing to identify a particular aspect of the pathology of meningiomas underdeveloped and mentioned in the literature.

Thus, using clinical, imaging and histopathological criteria, we managed to develop a scale for the particular analysis of meningiomas and, possibly, for the prognosis of their evolutionary aggression.

Inclusion criteria in the study are represented by (1) parenchymal invasion, (2) invasion of large blood vessels, (3) osteolysis without involvement of the external skull and (4) complete osteolysis with secondary aesthetic defect, were carefully selected using colleagues from the staff of the Radio-Imaging Laboratory and the Histopathology Service, emphasizing the importance of interdisciplinary collaboration for the benefit of patients. To the same extent, with the help of the above criteria, they have undergone adjustments compared to their original form. It should be noted that only cases that met at least 2 of the 4 criteria mentioned above were included in the study.

Between 01.01.2015 and 31.12.2019, within the Neurosurgery Service IV of the Emergency Clinical Hospital "Bagdasar-Arseni", 3149 brain tumors were treated, of which 1921 benign brain tumors (61%), in relative accordance with the data from literature.

Of the benign tumors (1921 cases), 1521 meningiomas were identified, representing 79.1% of all benign brain tumors and 48.3% of all brain tumors treated in our Service, a high percentage compared to 36.4% of all intracranial tumors described in the literature.

Using the 4 inclusion criteria mentioned before, a study group of 290 cases was gathered, which represents 19.06% of the total meningiomas treated. Breaking down the criteria for inclusion in the study, we obtained the following results:

- 225 cases, the equivalent of 77.58%, with parenchymal invasion;
- 204 cases with vascular invasion, the equivalent of 70.34% with vascular invasion;

 139 cases with bone invasion, the equivalent of 47,935% with bone invasion;

 61 cases with major aesthetic defects, the equivalent of 21.03%.

In terms of the number of study inclusion criteria met, we have the following statistical results:

 2 criteria in all 290 cases;

 3 criteria met by 216 cases;

 4 criteria were met in 61 cases.

The fact that the vast majority of the study group (74.4%) met at least 3 out of 4 criteria provides accuracy to the scale dedicated to this doctoral thesis.

In terms of gender distribution, we included in the study 182 female patients (62.75%) and 108 male patients (37.25%) in a ratio of 1.7 / 1, a statistical detail very close to literature.

The distribution by age groups shows a peak incidence in the 6th decade of life (50-60 years with a number of 145 patients, a percentage of 50%). Surprisingly, in the 3rd and 4th decades of life we have a number of 21 cases (7.2%) of the total cases included in the study. The other age groups are represented as follows:

 5th decade of life with 47 cases, percentage of 16.20%;

 7th decade of life with 66 cases, a percentage of 22.75%;

 8th decade of life with 8 cases, percentage of 2.75%;

 9th decade of life with 3 cases, a percentage of 1.03%.

The mean age of the patients was 56.9 years, with a minimum of 24 years and a maximum of 87 years. The mean age of the patients obtained in our study is similar to that of other epidemiological studies of intracranial tumors, 59 years.

In terms of the origin of the patients, there were 123 patients from rural areas (42.41%) and 167 from urban areas (57.59%). The geographical distribution by historical regions had the following distribution:

- 137 from the Moldova region, representing 47.24% of all patients;
- 85 from the Transylvania region, representing 29.31% of the total patients;
- 68 from the Muntenia region, representing 23.44% of the total number of patients.

Given the fact that from the point of view of the factors favoring the appearance of intracranial meningiomas, the ionizing radiation is in the first place, the results of these 2 statistical criteria tend to confirm the previously mentioned ones. The Chernobyl nuclear disaster, due to the geographical proximity of the regions in the northern half of Romania, and the natural barrier represented by the Carpathian Mountain Chain, may explain the higher incidence in the regions of Moldova and Transylvania, compared to the southern half of the country. Also, the fact that there is a higher percentage of patients from urban areas compared to rural areas, supports this hypothesis according to which ionizing radiation and air pollution are directly conducive to the appearance and development of this category of brain tumors.

Taking into account the fact that a large part of the patients (139 patients, representing 47.76% of cases, including 61 patients representing 21% of cases) had bone invasion and aesthetic deformities of the skull cap, we tried to assess the incidence of in the study group, based on the premise that patients with poor schooling may ignore clinical and local signs for a long time. However, 183 patients (representing 63.1%) of the cases are graduates of high school or higher education, which refutes the premise mentioned above.

From the point of view of the symptomatology at the admission in the Neurosurgery Service IV, we have the following statistical results:

- 246 patients with Intracranial Hypertension Syndrome, representing 84.82% of cases, and covering the full range of known signs and symptoms within this syndrome;
- 201 patients with Cerebral Lobe Syndromes, representing 69.31% of cases;

- 19 patients with Epilepsy, representing 6.5% of cases, the vast majority (15) being treated for Drug-Resistant Epilepsy without advanced imaging investigations;
- 27 patients, representing 9.31% of cases with Cranial Nerve Syndromes, out of the total number of cases of Infratentory Aggressive Meningiomas included in the study;
- 77 patients, representing 26.51% of cases, with other symptoms at admission, including Motor Deficiencies, Dizziness Syndromes or Vision Disorders;

Analyzing the comorbidities of patients in the hospital, we obtained the following results:

- 145 patients, representing 50% of cases, with cardiac comorbidities, a not at all surprising result considering the average age in the study group of 56.9 years;
- 84 patients, representing 29.96% of cases, with neurological comorbidities, resulting again within normal limits, given that 222 patients included in the study are aged between the 6th and 9th decade of life. ;
- 99 patients, representing 34.13% of cases with metabolic comorbidities, by this category referring strictly to diabetic patients, if we are talking about Type 1 or Type 2 Diabetes.
- 63 patients, representing 21.74% with obesity, taking into account all categories from Grade I Obesity to Morbid Obesity.
- 141 patients, representing 48.62% with other comorbidities, including all forms of Hepatitis, Renal Disorders and Associated Neoplasmic Pathology.

We note that of the 145 patients with associated cardiac pathology, 68 were on chronic anticoagulant therapy, and in all cases drug conversion was necessary in order to reduce the risk of intra- and postoperative bleeding.

From the point of view of the hospitalization period, the vast majority of patients were classified in the period 0-20 days, in a number of 197 which represents (67.93% of cases), also having 62 patients with a hospitalization between 20 and 30 days (21.3% of cases) and 31 patients with a hospital stay of more than 30 days (10.3%) of cases. It should be noted that the hospitalization period is directly proportional to the postoperative complications identified in the study, which will be detailed below.

In all 290 cases included in the study, patients underwent a Magnetic Resonance Imaging, 246 patients underwent a Brain Computed Tomography (representing 84.82% of cases), and in 115 cases a Cerebral Angiography was performed (representing 39.65%). All patients admitted and admitted to this study benefited from complete Laboratory Tests, Electrocardiogram, Pulmonary Radiography, Ophthalmic and ENT Consultations, as well as individualized specialty consultations for each patient according to the associated comorbidities.

Based on the imaging investigations performed, it was possible to classify the tumor lesions as follows:

- 17 tentorial lesions, representing 5.86% of cases;
- 36 infratentorial lesions, representing 12.41% of cases;
- 51 skull-base lesions, representing 17.58% of cases;
- 186 supratentorial lesions, representing 64.13% of cases.

Within the supratentorial location, the meningiomas were distributed as follows:

- 19 occipital lesions, representing 9.74% of cases with supratentorial location;
- 28 temporal lesions, representing 15.59% of cases with supratentorial localization;
- 41 parietal lesions, representing 22.04% of cases with supratentorial localization;
- 45 lesions with mixed localization, representing 24.19% of cases with supratentorial localization;
- 53 lesions with frontal location, representing 28.49% of cases with supratentorial location.

Using all the advanced imaging investigations, other important aspects for preoperative planning were determined, thus identifying the following:

- 57 cases with hydrocephalus according to the imaging criteria;
- 135 cases with the displacement of the midline according to the imaging criteria;
- 184 cases with ventricular compression according to imaging criteria.

Also, due to the fact that all patients benefited from Cerebral Magnetic Resonance Investigation, we were able to calculate the tumor size (diameter) in each case, with the following results:

- 3 lesions with a diameter between 10-20mm, representing 1.03% of cases;
- 9 lesions with a diameter between 20-30mm, representing 3.1% of cases;
- 140 lesions with a diameter between 30-40mm, representing 48.27% of cases;
- 89 cases with a diameter between 40-50mm, representing 30.68% of cases;
- 44 cases with a diameter between 50-60mm, representing 15.17% of cases;
- 16 cases with a diameter between 60-70mm, representing 5.51% of cases;
- 7 cases with a diameter between 70-80mm, representing 2.41% of cases;
- 2 cases with a diameter between 80-90mm, representing 0.68% of cases.

Thus, the average diameter of the lesions was about 42 mm in diameter. It should be noted that from an imaging point of view, the literature considers only malignant meningiomas to be aggressive, regardless of the radiological characteristics of the invasion at the level of the structures adjacent to the meningeal tumor lesions.

Of the 290 patients included in the study, admitted to the Neurosurgery Service IV, 281 cases were treated surgically (representing 96.89% of cases), the remaining 9 cases being treated conservatively. We mention that out of the 9 cases that did not undergo surgery, 7 had major contraindications, and 2 opted for conservative treatment.

Using the Simpson tumor resection scale on the degree of tumor resection, we obtained the following results:

- Simpson 0 - 114 cases, representing 39.31% of operated cases;
- Simpson 1 - 107 cases, representing 36.89% of operated cases;
- Simpson 2 - 50 cases, representing 17.24% of operated cases;
- Simpson 3 - 11 patients, representing 3.79% of operated cases;
- Simpson 4 - 8 patients representing 2.75% of operated cases;
- Simpson 5 - 1 patient representing 0.34% of operated cases.

In 45 of the 290 cases included in the study, it was necessary to perform a decompression craniectomy of necessity, representing 15.51% of the operated cases. Of these 45 patients, only 31 returned for further cranioplasty (68.88%), with the remaining 11 failing to undergo neurosurgical reassessments according to the department's protocols.

In terms of postoperative complications, we report the following:

- 22 postoperative arachnoid cysts, representing 7.82% of patients;
- 41 CSF fistulas, representing 14.59% of patients;
- 19 intraparenchymal hematomas in the tumor bed, representing 6.76% of patients;
- 23 post-surgical epilepsies, representing 8.18% of patients;
- 17 postoperative hydrocephalus, representing 6.04% of patients;
- 36 neurological aggravations, representing 12.81% of patients;
- 11 deaths, representing 3.91% of patients;

There was a close link between patients who developed postoperative complications such as intraparenchymal hematomas and the number of postoperative hydrocephalus and postoperative arachnoid cysts, respectively, 14 patients "ticking" all 3 types of postoperative complications.

The 11 patients who died were included in the 20 patients who benefited only from Simpson 3 to Simpson 5 tumor resection, all these 20 cases presenting intraoperative complications such as heavy bleeding or major heart disorders.

Analyzing the histopathological aspects, the classification of the operated aggressive meningiomas was divided as follows:

- meningiomatous meningiomas in 69 cases, representing 24.55%;
- fibrous meningiomas in 52 cases, representing 18.50%;
- transitional meningiomas in 13 cases, representing 4.62%;
- psmaomatous meningiomas in 11 cases, representing 3.91%;
- angiomatous meningiomas in 41 cases, representing 14.59%;
- microcystic meningiomas in 16 cases, representing 5.69%;
- secretory meningiomas in 17 cases, representing 6.04%;
- metaplastic meningiomas in 5 cases, representing 1.77%;
- atypical meningiomas in 38 cases, representing 13.52%;
- cordoid meningiomas in 6 cases, representing 2.13%;
- anaplastic meningiomas in 11 cases, representing 3.91%;
- rhabdoid meningiomas in 7 cases, representing 2.49%;
- papillary meningiomas in 4 cases, representing 1.42%;

Using the WHO scale for the classification of subtypes of meningiomas, we note that the histopathological subtypes considered malignant, aggressive by the degree of recurrence / tumor transformation represent a number of 68 cases out of the total of 281 cases that benefited from immunohistochemical examination that represents a percentage of 24.19%.

Also, of the 281 cases with certainty histopathological examination, 29 cases showed tumor recurrence (patients fully included in the tumor resection area Simpson 2 - Simpson 5) in 6 cases of transitional meningiomas and 23 atypical meningiomas. Also, in another 19 cases there was tumor progression to anaplastic meningiomas in 4 cases of transitional meningiomas, 15 atypical, all 19 patients being included in the above-mentioned group of patients who had tumor recurrence.

Thus, the percentage of tumor recurrence is 10.32%, and the percentage of patients who showed tumor progression is 6.76% at the time of writing this doctoral thesis.

From the follow-up point of view, we have the following statistical data:

- 271 patients presented to the 1-year control, representing 93.44% of cases;
- 226 patients presented to the control for 3 years, representing 77.93% of cases;
- 148 patients presented to the control for 5 years, representing 51.03% of cases;
- 137 patients underwent examinations after the 5-year period recommended by the protocols of the Neurosurgery Service IV.

However, taking into account that this study was conducted retrospectively between 01.01.2015 - 31.12.2019, the statistical data on the follow-up of patients are not complete, and may undergo further changes.

The postoperative evolution of the patients was evaluated using the Karnofsky Score, with the following results:

- score 100 in the case of 89 patients, representing 30.68%;
- score 90 in the case of 97 patients, representing 33.44%;
- score 80 in the case of 12 patients, representing 4.13%;

 score 50-70 in the case of 39 patients, representing 13.44%;

 score 0-40 in the case of 51 patients, representing 17.58%.

Statistically relevant data:

• Lowest Karnofsky presentation score: cordoid meningioma (Risk factor for severe presentation, p <0.1).

• Highest risk of progression: atypical meningioma (30.76%) (Risk factor for progression after incomplete resection, p <0.01).

• The risk of progression after subtotal resection is higher in men (p <0.05).

• Highest risk of recurrence: atypical meningioma (78.94%) (p <0.05).

• Improving postoperative Karnofsky score with statistically significant value (p <0.1).

CHAPTER 7. CONCLUSIONS

1. The scientific activity in the field of brain tumors in general, and brain meningiomas in particular, is in continuous progress, the present work being in the general direction of the world guidelines. Given the scientific inclination of the medical staff of the Neurosurgery Service IV, under the guidance of Professor Dr. Gorgan towards brain pathology, this thesis seeks to bring a new approach to how we look at cerebral meningiomas and how to manage these cases in the long term. medium and long.

2. The personal contribution, represented by the scale of inclusion in the study with the 4 mentioned categories, is a good indicator on the aggressiveness of these tumor lesions, considering the degree of invasion in the adjacent anatomical structures, with the difficulties thus caused, especially from the surgical point of view.

3. It should be emphasized that taking into account the 4 criteria of aggression, as well as the current approach from a histological and radio-imaging point of view, we could consider revising the existing criteria of aggression, especially given that the results obtained in this study are due to the interdisciplinary collaboration between neurosurgeon, radiologist and histopathologist.

4. It should also be borne in mind that the use of the nomenclature of aggressive meningioma can only be achieved after tumor resection and histopathological analysis, following the criteria of parenchimal, vascular and / or bone invasion. Also, performing the full range of imaging investigations (Cranial X-ray, Cerebral CT, Brain MRI and Cerebral Angiography) is especially useful for the neurosurgeon.

5. A statistically limiting issue is the lack of genetic analysis of the meningiomas included in the study, especially the Ki67 Factor, mainly due to the fact that patients have to perform these analyzes from their own funds, as this possibility does not exist at national level.

6. The high percentage of meningiomas included in the study, the high degree of recurrence and tumor transformation require us to continue to improve this scale in the coming years and to discover possible patterns to help improve postoperative outcomes given a quality of life as close to normal as possible for all our patients.

7. Surgery, regardless of the risks associated with it, should be the first-line therapeutic method, given that the quality of life assessment score (Karnofski) shows a marked postoperative improvement (improvement of the post-operative Karnofsky score with value statistically significant ($p < 0.1$)).

8. Considering the fact that from a statistical point of view meningiomas from the Atypical histological subtype present a high risk of both progression and tumor recurrence, we recommend the initiation of adjuvant treatments, especially Radiotherapy, immediately postoperatively.

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