FACULDADE DE MEDICINA
UNIVERSIDADE D
COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

MARIA EDUARDA CARVALHO LUCAS DE SÁ MARTA

World Health Organization Grade III Meningiomas: Current Knowledge and Retrospective Study at an Academic Medical Center

ARTIGO CIENTÍFICO ORIGINAL

ÁREA CIENTÍFICA DE NEUROCIRURGIA

Trabalho realizado sob a orientação de:

DOUTOR JOSÉ LUÍS MONTEIRO ALVES

PROFESSOR DOUTOR MARCOS DANIEL DE BRITO DA SILVA BARBOSA

MAIO/2020

Faculdade de Medicina da Universidade de Coimbra

World Health Organization Grade III Meningiomas: Current Knowledge and Retrospective Study at an Academic Medical Center

Meningiomas Grau III (Organização Mundial de Saúde): Conhecimento Atual e Estudo Retrospetivo num Centro Hospitalar Universitário

Maria Eduarda Carvalho Lucas de Sá Marta

Trabalho final do 6º ano médico na área científica de Neurocirurgia, orientado pelo Doutor José Luís Alves e pelo Professor Doutor Marcos Barbosa, apresentado à Faculdade de Medicina da Universidade de Coimbra com vista à atribuição do grau de Mestre no âmbito do ciclo de estudos do Mestrado Integrado em Medicina.

A thesis submitted to the Faculty of Medicine at the University of Coimbra for the degree of Master of Science in Medicine.

Maio de 2020 | May, 2020

FACULDADE DE MEDICINA
UNIVERSIDADE D
COIMBRA

DEDICATION

To my parents,

Who have made every one of my struggles their own as well.

To all the patients who ever let me learn with them,

I am forever grateful for your patience; I hope that one day Medicine can give answers to your questions, as much as you have answered ours.

Acknowledgements

No one can go far without a good amount of help. That being said, I would like to thank Dr. José Luís Alves, who was kind enough to accept me as his student in this project and was always there to answer my questions.

I was also lucky enough to have Professor Marcos Barbosa take me as one of his supervised students, and I cannot say how grateful I am for his understanding and willingness to help me when I most needed it.

I would also like to thank Dr. Olinda Rebelo for helping with the retrieval of the pathology reports of the patients involved in the clinical study that was developed for this thesis. I am also grateful for Dr. Hermínio Tão's input on this project.

In addition, I thank Professor Natália António whose humanity was unparalleled when she understood the difficulties I was faced with and did not hesitate to offer her support.

I am also grateful to the neurosurgery team at Brigham and Women's Hospital/ Harvard Medical School for the possibility of discussing the project design of this study during Neurosurgery Grand Rounds and for giving me advice on how I should better conduct research on WHO grade III meningiomas.

Finally, a big "thank you" to those who always cared for me, and who always will: my parents.

The original research article that is part of this thesis has been prepared for submission to the journal *World Neurosurgery* and therefore complies with its submission guidelines.

Abstract

Meningiomas are the most common primary brain tumors (37.6% of all central nervous system tumors), according to recent data from the Central Brain Tumor Registry of the United States (CBTRUS). The vast majority of meningiomas are considered to be benign tumors (World Health Organization [WHO] grade I). However, around 20% of meningiomas display aggressive behavior and have higher rates of recurrence. These meningiomas are classified as WHO grade II or grade III meningiomas, the latter being the most aggressive subtype. Representing 1.7% of all the meningiomas with documented WHO grade, grade III meningiomas are associated with a much worse prognosis.

Due to their rarity, much remains to be known about WHO grade III meningiomas. The aim of this work was therefore twofold: first, to review the current knowledge on WHO grade III meningiomas; second, to conduct a retrospective review of WHO grade III (anaplastic, rhabdoid and papillary) meningioma cases at the Coimbra University Hospital Center/Centro Hospitalar e Universitário de Coimbra (CHUC).

In this retrospective clinical study, we found that, of the 26 patients included in the final analysis, 23 (88.5%) had anaplastic meningiomas, 2 (7.7%) had papillary meningiomas, and 1 (3.8%) had a rhabdoid meningioma. Median overall survival and median progression-free survival were 2.45 and 1.22 years, respectively. Overall survival rates at 1, 2 and 5 years were 73%, 57% and 35%, respectively. There was a trend toward improved overall survival with gross total resection (Simpson grades I+II) versus subtotal resection (Simpson grade IV), but the difference failed to reach statistical significance. Adjuvant radiotherapy correlated with improved survival in patients with subtotally resected meningiomas, but not in patients whose meningiomas were gross totally resected.

WHO Grade III meningiomas portend a devastating prognosis and the impact of extent of resection and adjuvant therapies on the survival of these patients still needs further clarification. We thus hope to have contributed to the bulk of knowledge on the clinical outcome of WHO grade III meningiomas.

Keywords: Malignant Meningioma; Papillary Meningioma; Prognosis; Radiotherapy; Local Neoplasm Recurrence

Resumo

Os meningiomas são os tumores cerebrais primários mais comuns (37,6% de todos os tumores do sistema nervoso central), de acordo com dados recentes do Central Brain Tumor Registry of the United States (CBTRUS). Os meningiomas, na sua vasta maioria, são considerados como sendo tumores benignos (grau I da Organização Mundial de Saúde [OMS]). Contudo, cerca de 20% dos meningiomas têm um comportamento agressivo e taxas mais elevadas de recorrência. Estes meningiomas são classificados como de grau II ou grau III da OMS, sendo o último o subtipo mais agressivo. Correspondendo a 1,7% de todos os meningiomas com grau da OMS documentado, os meningiomas grau III da OMS estão associados a um prognóstico muito mais reservado.

Devido à sua raridade, há ainda muito a saber acerca dos meningiomas grau III. O objetivo deste trabalho foi então duplo: primeiro, rever o conhecimento atual sobre meningiomas grau III da OMS; segundo, levar a cabo um estudo retrospetivo de casos de meningiomas grau III (anaplásicos, rabdoides e papilares) no Centro Hospitalar e Universitário de Coimbra (CHUC).

Neste estudo clínico retrospetivo, observou-se que, dos 26 doentes incluídos na análise final, 23 (88,5%) tinham meningiomas anaplásicos, 2 (7,7%) tinham meningiomas papilares e 1 (3,8%) tinha um meningioma rabdoide. As medianas da sobrevida global e da sobrevida livre de recorrência foram 2,45 e 1,22 anos, respetivamente. As taxas de sobrevida global a 1, 2 e 5 anos foram de 73%, 57% e 35%, respetivamente. Houve uma sugestão de melhoria na sobrevida global com resseção macroscopicamente total (exéreses I e II de Simpson) comparando com resseção subtotal (exérese IV de Simpson), mas a diferença não foi estatisticamente significativa. O uso de radioterapia adjuvante após cirurgia resultou numa maior sobrevida em doentes com meningiomas cuja resseção foi subtotal, mas não em doentes com resseção macroscopicamente total.

Os meningiomas grau III da OMS associam-se a um prognóstico devastador e o impacto do grau de resseção e de terapias adjuvantes necessita ainda de maior clarificação. Espera-se, pois, que com este trabalho tenha sido feita uma adição ao corpo de conhecimento sobre o comportamento clínico dos meningiomas grau III da OMS.

Palavras-chave: Meningioma Maligno; Anaplasia; Prognóstico; Radioterapia; Recidiva Local de Neoplasia

Contents

Abbreviations

CBTRUS – Central Brain Tumor Registry of the United States

CSCs – Cancer stem cells

CT – Computed tomography

CTLA-4 – Cytotoxic T-lymphocyte antigen 4

GTR – Gross total resection

Gy – Gray

HPF – High-power fields

KFS – Karnofsky Performance Status

MRI – Magnetic resonance imaging

PD-1 – Programmed death 1

PD-L1 – Programmed death-ligand 1

PET/CT – Positron emission tomography/computed tomography

Refs. – References

STR – Subtotal resection

TERTp – Telomerase reverse transcriptase promoter

USA – United States of America

WHO – World Health Organization

Part A. World Health Organization Grade III Meningiomas: Current Knowledge

A.1. Introduction

Meningiomas are the most common primary intracranial tumor according to the Central Brain Tumor Registry of the United States (CBTRUS).[1] Although generally considered to be benign and amenable to cure through surgical treatment, a small fraction of these patients harbor meningiomas associated with high rates of morbidity and mortality, for which optimal treatment has not yet been established. The most aggressive of these meningiomas are classified as grade III meningiomas under the World Health Organization (WHO) Classification of Tumors of the Central Nervous System.[2]

In this narrative review, we aimed to summarize much of what is known about WHO grade III meningiomas, namely their brief history, cellular origin, genetics, epidemiology, clinical features, therapeutic options and prognosis according to previously published studies. We finish our review by discussing possible new avenues of research in this field.

A.2. Methods

A wide search using the PubMed/MEDLINE® database, looking at articles from database inception until April 2020, was carried out. The following search terms were used: “meningioma*” AND (“grade 3” OR "grade iii" OR "anaplastic" OR "malignant" OR "rhabdoid" OR "papillary") (* was used for truncation in order to include both plural and singular forms). Articles with pertinent titles were analyzed for possible posterior inclusion in this narrative review. Secondary references found through the retrieved articles (both through the references section and articles which cited the primary articles) were also analyzed if relevant. Textbooks on meningiomas that are indexed in Google Books were searched for additional information. Besides English, articles which were written in Portuguese, French, German or Spanish were also included in case they were deemed relevant.

A.3. Results

A.3.1. Brief History of Meningiomas and Their Classification

The term “meningioma” was first coined in 1922 by Harvey Cushing[3], the so-called “Father of Neurosurgery” (Fig. 1).

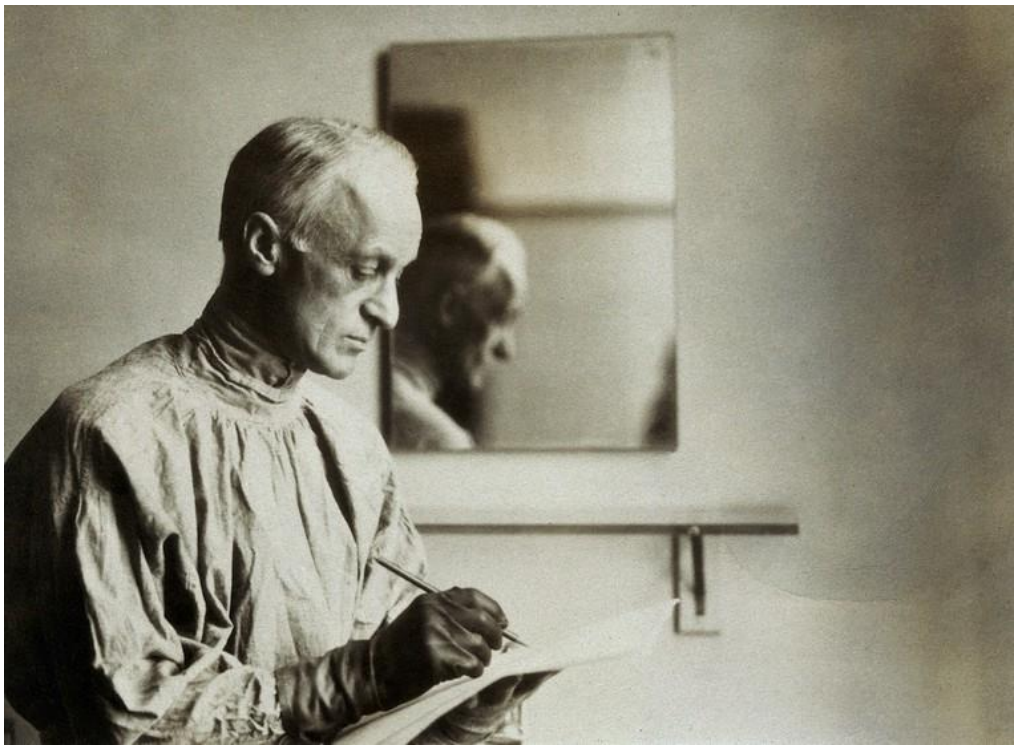


Figure 1 – Harvey Cushing (unknown date). **Credit**: Harvey Williams Cushing. Photograph by W.(?)W.B. Credit: Wellcome Collection. CC BY

Meningiomas, however, have probably been around us ever since the beginning of humankind, as can be attested by the hyperostosis characteristic of meningiomas present in several human skulls from prehistoric times.[4]

A Swiss physician named Felix Platter is thought to have given the first description of a meningioma.[4, 5] A translation of Platter’s description in 1614 (taken from Al-Rodhan and Law’s article[4]) is the following:

> … a round fleshy tumor, like an acorn. It was hard and full of holes and was as large as a medium-sized apple. It was covered with its own membrane and was entwined with veins. However, it was free of all connections with the matter of the brain, so much so that when it was removed by hand, it left behind a remarkable cavity.

It thus seems that Plater was referring to an encapsulated meningioma.[4]

The history of the nomenclature of meningiomas is complex, with more than 40 designations given to this entity throughout the years.[4] Cushing's term is the only one that is consistently used nowadays.

Also convoluted are the many attempts at classifying meningiomas, the first one being Virchow's proposal of classification, in 1863.[4] Cushing himself, together with Louise Eisenhardt, developed a classification scheme, published in 1938, that was one of the greatest single advances in our understanding of meningiomas.[6]

The current prevailing classification of meningiomas corresponds to the 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System.[2] The WHO classification allowed for an homogenization in the way tumors of the central nervous system are classified across different countries, thereby facilitating collaborative efforts.[7] Below is a table summarizing the evolution of the WHO classification of meningiomas.

Table 1 – Classification of meningiomas according to the World Health Organization throughout the years. Changes in each edition relative to the previous one are underlined.

Year	Edition	Editors	Classification relative to meningiomas	Refs.
1979	1st	Zülch	*Grade I*: meningotheliomatous; fibrous (fibroblastic); transitional (mixed); psammomatous; angiomatous; hemangioblastic *Grade II*: hemangiopericytic *Grades II and III*: papillary; anaplastic (malignant)	(8)
1993	2nd	Kleihues, Burger, Scheithauer	*Grade I*: meningothelial; fibrous (fibroblastic); transitional (mixed); psammomatous; angiomatous; <u>microcystic; secretory; clear cell; chordoid; lymphoplasmacyte-rich; metaplastic</u> *Grade II*: <u>atypical</u> *Grade II or III*: papillary *Grade <u>III</u>: <u>anaplastic</u>* (malignant)	(7)
2000	3rd	Kleihues, Cavenee	*Grade I*: meningothelial; fibrous (fibroblastic); transitional (mixed); psammomatous; angiomatous; microcystic; secretory; lymphoplasmacyte-rich; metaplastic *Grade <u>II</u>:* atypical; <u>clear cell (intracranial); chordoid</u> *Grade <u>III</u>: <u>rhabdoid</u>*; <u>papillary</u>; anaplastic (malignant)	(9, 10)

2007	4th	Louis, Ohgaki, Wiestler, Cavenee	No substantial changes relative to previous edition [11]	(12, 13)
2016	Revised 4th	Louis, Ohgaki, Wiestler, Cavenee	No substantial changes relative to previous edition [14]	(2)

Looking at the evolution of the WHO classification of central nervous tumors, one can conclude that it has been relatively stable for meningiomas since 2000. An important change in the 2000 classification scheme was the removal of brain invasion as a criterion for anaplastic meningiomas, as it was concluded that this should be instead a criterion for WHO grade II meningiomas.[15] Also, stricter criteria for classifying meningiomas as WHO grade III were added, including a clear mitotic count cut-off (at least 20 mitoses per 10 high-power fields, HPF) or overtly malignant sarcoma-, carcinoma-, or melanoma-like cytology.[6] This change was implemented after a large study from the Mayo Clinic showed that nonanaplastic meningiomas that invaded the brain behaved similarly to grade II meningiomas in terms of prognosis.[16]

Although one should always aim to follow the most recent WHO classification, it is important to be acquainted with the evolution of this classification scheme as to understand older (and even fairly recent, if not carefully updated) publications in the field of meningiomas. Indeed, some of these articles may still use terms of old classification schemes. Being familiar with the history of the WHO classification also allows for a better understanding of old medical records of patients diagnosed with meningiomas.

The editorial board responsible for the WHO Classification of Tumors of the Central Nervous System held an online meeting on March 19-20, 2020 in preparation for the 5th edition of this classification scheme.[17]

A.3.2. Nomenclature

The terminology used across various research articles on WHO Grade III meningiomas is not perfectly uniform. In most cases, articles do not strictly adhere to the WHO Classification of Tumors in the Central Nervous System, seeing that grade III meningiomas as a whole are normally referred to as “malignant meningiomas”. However, the WHO classification states that

anaplastic meningiomas are synonymous with malignant meningiomas, and these are only a subset of grade III meningiomas, the other WHO grade III meningioma subtypes being papillary and rhabdoid meningiomas.[2]

Hence, according to the text of the 4th edition (revised in 2016) of the WHO Classification of Tumors in the Central Nervous System[2], one can only assume the following:

Grade III meningiomas (according to WHO)	Anaplastic=malignant
	Rhabdoid
	Papillary

A common use (although not universal and not clearly conforming to the former classification) of "malignant meningiomas" is the following[6]:

Grade III/Malignant meningiomas (common use, **not clearly** mentioned in the WHO Classification)	Anaplastic
	Rhabdoid
	Papillary

There are even some research groups that assume that the term anaplastic is synonymous with grade III meningiomas, meaning that anaplastic meningiomas would include the rhabdoid and papillary meningiomas as well.[18] There seems to be an excessively liberal use of the term "anaplastic", and hence we only mention this fact as every researcher in this area should be aware of this possibility.

In clinical practice, the use of the term "high-grade meningioma" is generally accepted as synonymous with the combined group of WHO grade II and grade III meningiomas.

A.3.3. Epidemiology and Risk Factors for Meningiomas

A.3.3.1. General Epidemiology of Meningiomas

In terms of epidemiology, the most accurate and complete information comes from the United States of America (USA), specifically from the Central Brain Tumor Registry of the United States (CBTRUS). Europe is still lagging behind in terms of a centralized European tumor registry that can provide detailed information on the epidemiology of meningiomas.

It is well established that meningiomas in general are more common in women than they are in men. In the USA, non-malignant meningiomas were found to be 2.32 times more common in females than in males. The incidence of this tumor was also found to be higher in Blacks

than in Whites. Meningiomas are primarily diagnosed at older ages (median age of 66 years).[1] Meningiomas are thus uncommon in children, but very aggressive meningiomas have been diagnosed in patients as young as 2 or 3 years old.[19, 20]

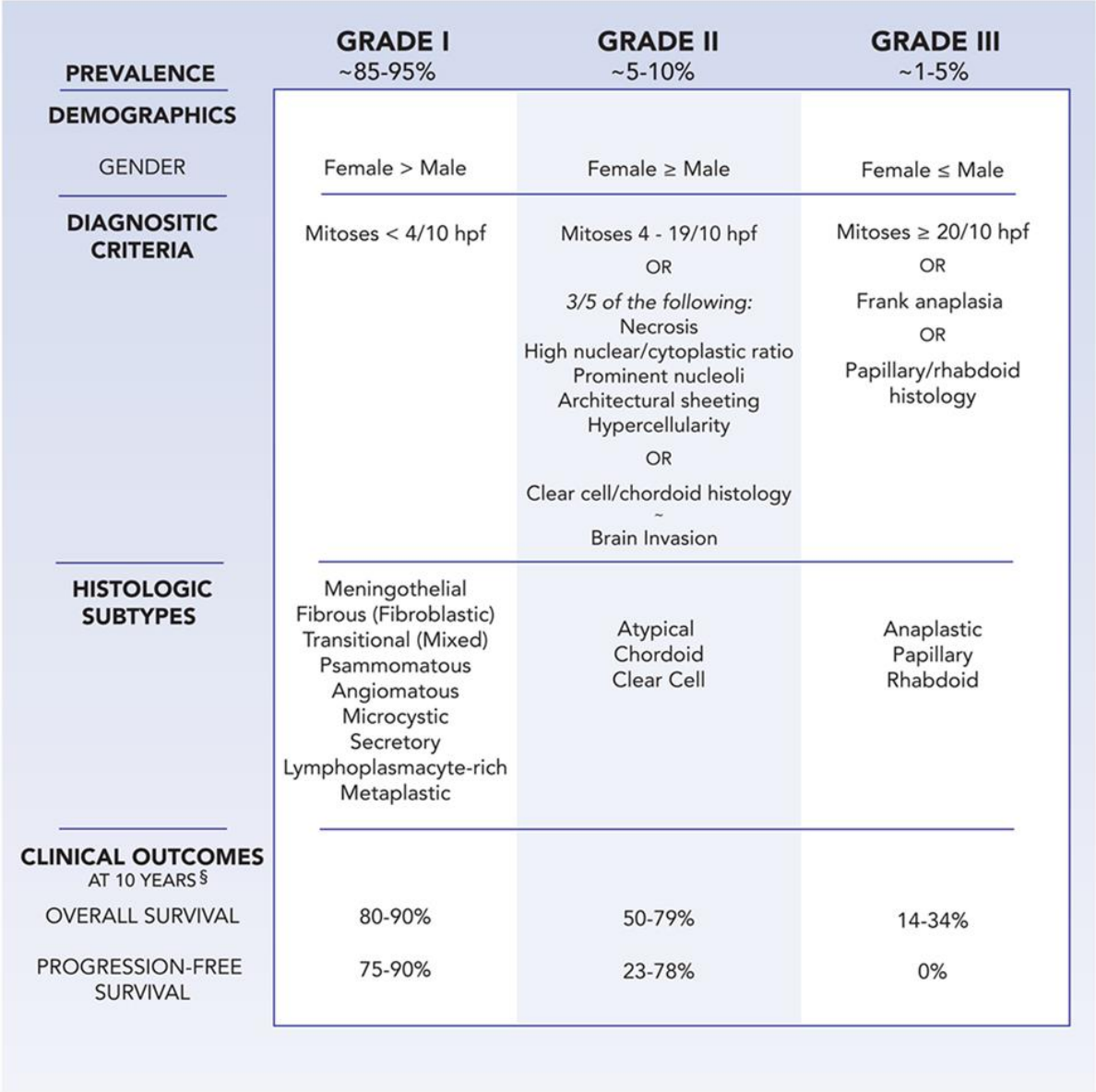
Among the meningiomas with documented WHO grade in the United States, 80.5% were WHO grade I, 17.7% were WHO grade II and 1.7% were WHO grade III.[1]

The average annual age-adjusted incidence rate of all meningiomas in the USA during 2012-2016 was 8.58 per 100,000 population.[1] Age-adjusted incidence rate for WHO grade III meningiomas was (per year, on average) 0.07 per 100,000 population over the period of 2000-2010.[21] That is, almost 1 person per million in the general population was diagnosed with a WHO grade III meningioma in the USA each year during that period.

A.3.3.2. Meningiomas and Ionizing Radiation

The most recognized etiological factor for meningiomas is past exposure to ionizing radiation, with a six- to ten-fold higher risk reported in atomic bomb survivors. Children who were given radiation therapy for scalp ringworm in Israel in the mid-20th century were also observed to have a ten-fold increase in the risk of having a meningioma later on in life. Even full-mouth X-rays have been associated with an increased risk of having a meningioma.[22]

Table 2 – Demographics relative to the 4th edition (2007) WHO classification of Central Nervous Tumors. © 2016 Bi, Zhang, Wu, Mei and Dunn. Reproduction permitted under the Creative Commons Attribution License (CC BY).[23]



	GRADE I ~85-95%	GRADE II ~5-10%	GRADE III ~1-5%
PREVALENCE			
DEMOGRAPHICS			
GENDER	Female > Male	Female ≥ Male	Female ≤ Male
DIAGNOSITIC CRITERIA	Mitoses < 4/10 hpf	Mitoses 4 - 19/10 hpf OR *3/5 of the following:* Necrosis High nuclear/cytoplastic ratio Prominent nucleoli Architectural sheeting Hypercellularity OR Clear cell/chordoid histology ~ Brain Invasion	Mitoses ≥ 20/10 hpf OR Frank anaplasia OR Papillary/rhabdoid histology
HISTOLOGIC SUBTYPES	Meningothelial Fibrous (Fibroblastic) Transitional (Mixed) Psammomatous Angiomatous Microcystic Secretory Lymphoplasmacyte-rich Metaplastic	Atypical Chordoid Clear Cell	Anaplastic Papillary Rhabdoid
CLINICAL OUTCOMES AT 10 YEARS §			
OVERALL SURVIVAL	80-90%	50-79%	14-34%
PROGRESSION-FREE SURVIVAL	75-90%	23-78%	0%

A.3.3.3. Grade III Meningiomas: Hormonal Factors and Gender

A relationship between pregnancy and the rapid growth of meningiomas has been suggested for more than a century.[24] One of the putative reasons is the presence of progesterone receptors in meningiomas which are sensitive to the rise of progesterone levels during pregnancy, thereby possibly leading to an increased rate of growth of these tumors. Other researchers defend that the growth of these meningiomas during pregnancy is not fueled by hormones, but by vascular or hemodynamic changes instead.[25]

Grade III meningiomas diagnosed during pregnancy are very rare in the literature. A case of papillary meningioma that presented during pregnancy has, however, been reported in a 25-year-old female.[26] We are not aware of any study that has specifically addressed the question of whether WHO grade III meningiomas are indeed less frequent in pregnant females than in the general female population of reproductive age.

Another interesting finding that might help shed some light on this topic is the association between absence of progesterone receptors in meningiomas and a higher risk of tumor recurrence.[27, 28] Kuroi et al. showed that skull-base meningiomas, which were more frequently benign that non-skull base meningiomas, had a higher progesterone receptor expression when compared to the latter group.[29]

On the other hand, the role of estrogen receptors in meningiomas is more debatable, but there is some evidence that they have the opposite role as a prognostic indicator than that of progesterone receptors. Hence, despite the fact that few tumors express positivity for estrogen receptors, the latter seem to be associated with a more aggressive meningioma behavior.[28-30]

Whatever the roles of hormonal factors may be in the pathogenesis of meningiomas, it is true that the female/male ratio is equal to 1 or even less than 1 for WHO grade III meningiomas (Table 2).[23]

That being said, the question arises of whether WHO grade III meningiomas are indeed “less female, more aggressive” tumors because of their rapid growth that seems to be independent of hormonal factors.[31]

A.3.3.4. High-Grade Meningiomas and Location

Several research groups have published evidence that non-skull base meningiomas are more likely to be high-grade when compared to skull base meningiomas.[29, 32, 33] Moreover, it also seems that high-grade meningiomas are also rarer in the spine.[33]

A.3.3.5. High-Grade Meningiomas and the Elderly

If malignancies[34] and meningiomas[35] in general are already considered to be diseases whose risk is increased with greater age, the impact of advanced age on the probability of one being diagnosed with a high-grade meningioma seems to be even more significant. Indeed, the mean age at diagnosis of high-grade meningiomas (WHO grades II and III) has been reported to be statistically significantly higher than that for WHO grade I meningiomas, with the

mean age of diagnosis being 55.1, 59.0 and 64.3 years for WHO grades I, II and III meningiomas, respectively.[36] Another study found that the proportion of patients diagnosed with high-grade meningiomas was significantly higher in the group of patients ≥75 years old than in patients <75 years old (44% vs. 14%).[37]

A.3.4. Origin and Genetics of Meningiomas

A.3.4.1. Cellular Origin of Meningiomas

Meningiomas are thought to arise from arachnoid cap cells, being therefore derived from the neuroectoderm, although their origin remains to be completely elucidated even as of today. This hypothesis comes from histologic and ultrastructural similarities between arachnoid cells and meningiomas. Both normal arachnoid and meningioma cells display psammoma bodies and generally express E-cadherin, although meningioma cells display fewer interdigitations and junctional complexes.[38] The latter correspond to structures between adjacent cells that comprise tight junctions, anchoring junctions and desmosomes.[39]

A.3.4.2. Genetics of Meningiomas

One of the most well established mutations in meningiomas is related to the *NF2* gene (the "Merlin" gene) located in chromosome 22. Mutations in this gene are known to cause neurofibromatosis type II, a genetic syndrome in which 50-75% of patients develop at least one meningioma.[23]

Despite the fact that meningiomas can be one of the clinical findings in genetic syndromes, the same mutations (such as the loss of the *NF2* gene) are to be found in 40-60% of sporadic tumors. Next-generation sequencing has more recently identified mutations present in 40% of tumors, namely TNF receptor-associated factor 7 (*TRAF7*), the pluripotency transcription factor Kruppel-like factor 4 (*KLF4*), the proto-oncogene v-Akt murine thymoma viral oncogene homolog 1 (*AKT1*), the Hedgehog pathway signaling member Smoothened (*SMO*), and the oncogene *PIK3CA* (Fig. 2).[23]

Although further research is needed, studies have found that specific mutations in *NF2*, ERBB, KAT6B, and TET2 may be associated with anaplastic meningiomas.[40] The methylation and/or mutation of the telomerase reverse transcriptase promoter (TERTp), leading to an overexpression of TERT, also seems to be present in the majority of anaplastic meningiomas.[41]

Regarding meningiomas in general, family history (e.g., having a first degree relative diagnosed with a meningioma) has been shown to result in increased risk for developing this tumor, although family-based linkage studies are still insufficient in this field.[22] From the clinical point of view, it is very rare to see families with multiple members diagnosed with meningiomas. This situation is almost exclusively seen in families with *NF2* mutations.[22]

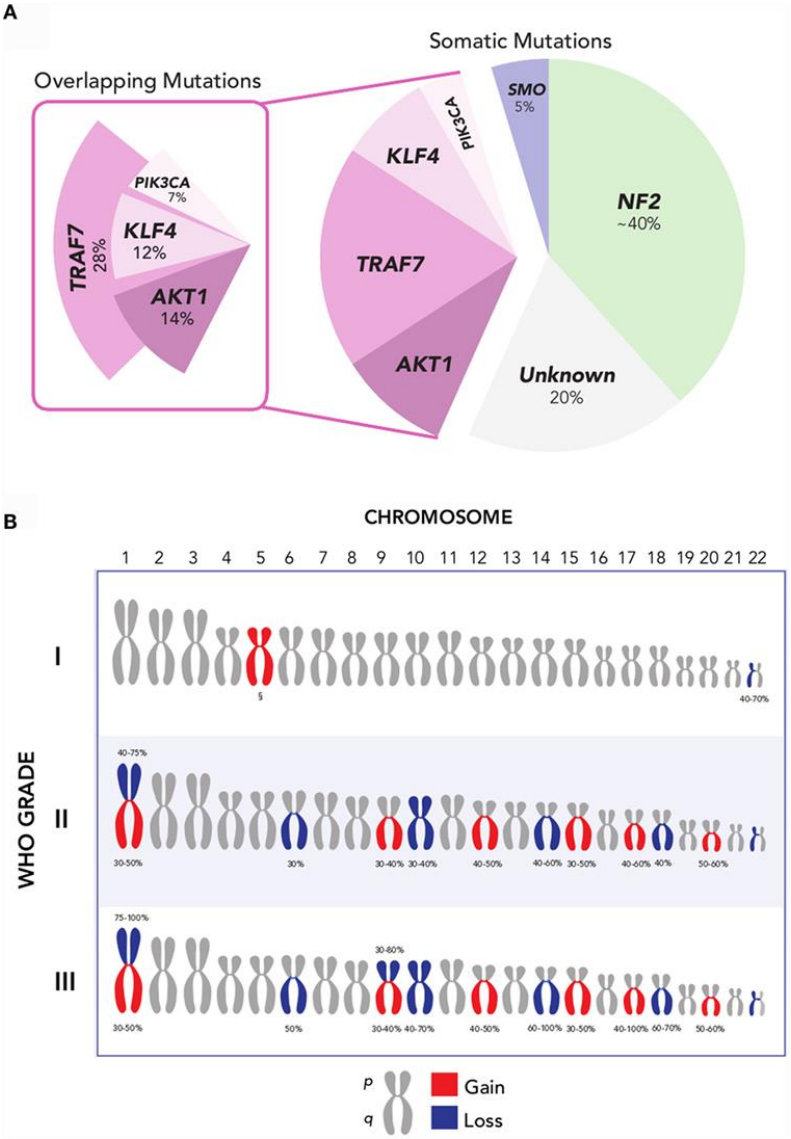


Figure 2 – **A.** Relative frequency of mutations in WHO grade I meningiomas. Mutations in AKT1, KLF4, and PIK3CA overlap with TRAF7, but not with each other, and largely occur in a mutually exclusive pattern with NF2 and SMO. **B.** Chromosomal copy number alterations in meningioma. It is evident that high-grade meningiomas display a greater number of copy number gains (red) and losses (blue). © 2016 Bi, Zhang, Wu, Mei and Dunn. Reproduction permitted under the Creative Commons Attribution License (CC BY).[23]

The genetic conditions currently known to be associated with meningiomas are neurofibromatosis type 2 (the most common disorder associated with these tumors), Werner's syndrome, von Hippel Lindau disease, Rubinstein-Taybi syndrome, neurofibromatosis type 1, Li Fraumeni syndrome, multiple endocrine neoplasia type 1 (MEN1) and Gardner syndrome.[38] Because not many genetic diseases are known to be associated with aggressive types of meningiomas, the latter seem to be mostly sporadic in nature and would fit the hypothesis that an increased burden of mutations with advancing age would predispose a person to a more aggressive type of meningioma (as noted in section A.3.3.5).

A.3.4.3. Cancer Stem Cells in Meningiomas

Cancer stem cells (CSCs) are a group of cells thought to be responsible for the initiation and continuous renovation of malignancies, analogously to the function of normal stem cells in the renewal of a cell population in tissues which underwent some type of damage.[42]

The existence of cancer stem cells in meningiomas, and particularly in high-grade variants which are more likely to recur, might therefore prove an interesting area of investigation. Unfortunately, little research effort has been devoted to this topic. Nevertheless, there is some evidence from pre-clinical studies that meningioma stem cells express CD133, SOX2 and possibly nestin. Other markers include proteins OCT4, NANOG, c-Myc, KLF4 and vimentin.[43] These markers seem to be expressed differently according to meningioma grade. For example, c-Myc[44] and NANOG[45] are more frequently expressed by high-grade meningiomas while KLF4 expression is lower in anaplastic meningiomas[46].

A.3.5. Clinical Features and Diagnosis of WHO Grade III Meningiomas

A.3.5.1. Clinical Features of Meningiomas

The disease manifestations of meningiomas are nonspecific and varied, and also depend on the location of the meningioma. The most common symptoms are headaches, seizures and personality changes. On physical exam, hemiparesis, sensory deficits and ataxia may be noted. In the case of spinal meningiomas, spinal cord compression may lead to motor and sensory deficits.[6]

A.3.5.2. Diagnosis of Malignant Meningiomas

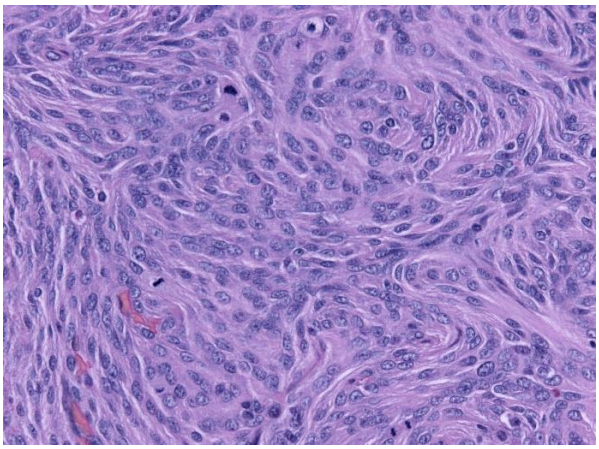
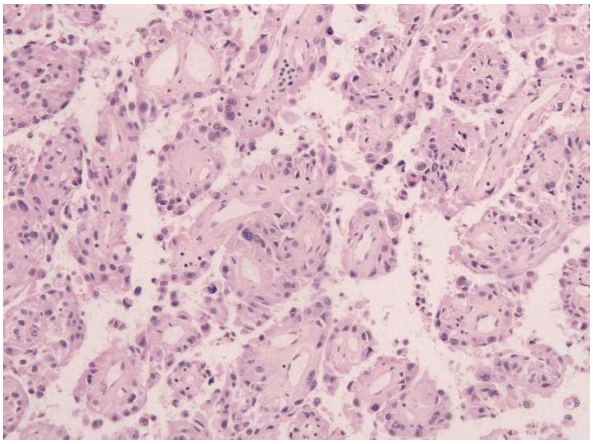
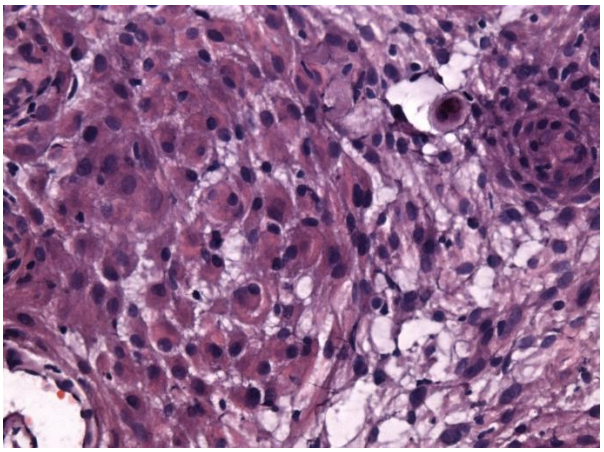
After suspicion of a space-occupying lesion in the brain (in the case of intracranial meningiomas), the imaging modality of choice is normally a noncontrast head computed tomography (CT) scan. Meningiomas are normally isodense to gray matter on noncontrast CT. However, when contrast is used, meningiomas are known to enhance strongly in CT and magnetic resonance imaging (MRI) images. The famous “dural tail sign” (although not pathognomonic for meningiomas) is helpful in the diagnostic work-up of meningiomas as it indicates that the space-occupying lesion is extra-axial.[6]

Despite the characteristic imaging features of meningiomas, a diagnosis can only be established by surgery. This is even more true for WHO grade III meningiomas, since no imaging features to date can accurately predict tumor grade and its aggressiveness.[23]

Surgical neuropathology is thus fundamental in providing the neurosurgeon with a definitive diagnosis, namely the WHO grading of the meningioma, thereby providing information on expected clinical outcome and prognosis of meningioma patients.

The most recent WHO classification of central nervous tumors has already been addressed in former sections. Focusing now on WHO grade III meningiomas specifically, table 3 provides an overview of the three subtypes currently considered as the most aggressive meningioma histologic variants: anaplastic (malignant), papillary and rhabdoid meningiomas.

Table 3 – Definition of WHO grade III meningiomas (according to the 2016 WHO Classification[2])

Anaplastic (malignant)  Figure 3 (by Jensflorian / CC BY-SA)	Overtly malignant Cytology (resembling that of carcinoma, melanoma, or high-grade sarcoma) and/or markedly elevated mitotic activity (> 20 mitoses per 10 HPF). Most show a Ki-67 proliferation index > 20%.
Papillary  Figure 4 (by Jensflorian / CC BY-SA)	Perivascular pseudopapillary pattern that constitutes the majority of the tumor. Loss of cohesion, clinging of tumor cells to blood vessels, and a nucleus-free perivascular zone which resembles pseudorosettes of ependymoma.
Rhabdoid  Figure 5 (by Jensflorian / CC BY-SA)	Consists mainly of rhabdoid cells: plump cells with eccentric nuclei, open chromatin, a prominent nucleolus, and prominent eosinophilic paranuclear inclusions. These cells can appear as discernible whorled fibrils, or compact and waxy.

A.3.5.3. Metastases of WHO Grade III Meningiomas

Metastases arising from meningiomas in general are rare, but seem to be much more frequent in the case of grade III meningiomas. The most common reported sites for meningioma metastases (according to a review by Surov et al.[47]) are lung, bone, spine and liver. Still, one must take into account that, because meningioma metastases are not actively screened for, we do not have a clear idea of what percentage of patients with grade III meningiomas actually have metastases and which locations indeed most frequently harbor these metastases.

Kessler, Garzón-Muvdi et al. published a case series which included 4 patients with metastasized grade III meningioma and observed that 3 of them had metastases to the lung and the remaining patient metastases to the liver and spine.[48]

Metastases of WHO grade III meningiomas to lymph nodes have been reported.[49] However, disseminated disease has also been found to occur in WHO grade I meningiomas.[50]

PET/CT (specifically with (68)Ga-DOTANOC) has been used to detect meningioma metastases[51], but its routine use in WHO grade III meningiomas is still far from being widely accepted into clinical practice and its utility is still questioned.

A.3.6. Therapeutic Options for WHO Grade III Meningiomas

A.3.6.1. Surgery for Meningiomas and the Simpson Grading System

Surgery is the mainstay of treatment for symptomatic and/or enlarging meningiomas, irrespective of WHO grade.[52] In 1957, Simpson defined 5 grades of resection and their respective rates of recurrence (Table 4).[53] Ever since this germinal publication, the Simpson grading scheme has remained almost undisputed and is nowadays widely used by neurosurgeons all over the world. In 1986, Borovich et al. suggested that a “grade zero” resection be added[54] and Kinjo, Al-Mefty and Kanaan showed evidence of its possible use[55], but the neurosurgical community has not universally accepted this modification.

In the case of benign (WHO grade I) meningiomas, complete resection of the tumor can be considered curative, although recurrence may still occur in some cases. However, WHO grade III meningiomas may more frequently display bone, brain and venous sinus invasion, precluding many times a Simpson grade I resection from being achieved. In cases where only a subtotal resection can be performed, patients with WHO grade III meningiomas normally undergo radiotherapy (Fig. 6). [52]

Table 4 – Modified Simpson grading scheme for extent of resection of meningiomas.

Simpson grade	Extent of resection	Recurrence rate at 5 years
0	Total removal of the tumor, dural attachment, and infiltrated bone with additional resection of a 2-cm dural margin	0%
1	Total removal of the tumor, dural attachment, and infiltrated bone	9%
2	Total removal of the tumor, dural attachment coagulated	19%
3	Total removal of the tumor, without resection nor coagulation of the dura/infiltrated bone	29%
4	Partial resection of the tumor	39%
5	Decompression (biopsy)	Ns

Grade zero was a modification suggested by Borovich[54] and solidified by Kinjo, Al-Mefty and Kanaan[55]. [52]

A.3.6.2. Radiotherapy

Several radiotherapy modalities are currently in use for WHO grade III meningioma patients. Examples include hypo-fractionated radiation therapy, photon based stereotactic radiosurgery (gamma knife), proton radiation and brachytherapy.[56] Of these, hypo-fractioned radiotherapy is probably the most accessible to patients in countries where the newest radiotherapeutic techniques are not yet available. A total dose of 60 Gray (Gy) divided by fractions of 2 Gy is routinely used after subtotal resections.[52]

These treatments do not come without associated risks: radiation necrosis, worsening of peritumoral edema, wound complications, optic neuropathy and even cranial nerve palsy are all possible consequences of radiation therapy.[56]

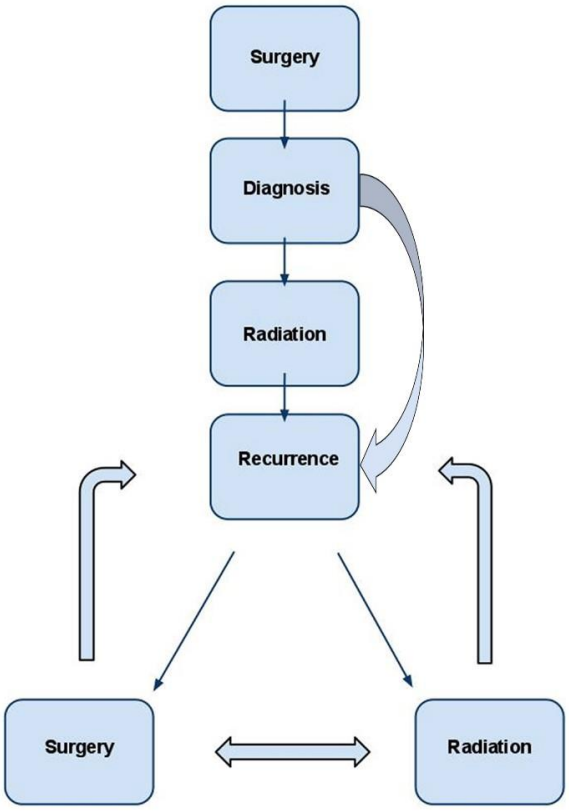


Figure 6 – Management strategy for WHO grade II and grade III meningiomas. Because there have been no randomized clinical trials (e.g., robust evidence is lacking in terms of survival benefit) for grade III meningiomas, and according to the patient's overall health status and wishes, radiotherapy may not be administered after surgery. Adapted from © 2013 Walcott, Nahed, Brastianos and Loeffler. Reproduction permitted under the Creative Commons Attribution License (CC BY).[56]

A.3.6.3. Chemotherapy

The role of chemotherapy in the management of meningiomas is not well defined and temozolomide has failed to show significant improvement in the survival of these patients.[38] Hydroxyurea might prove of some efficacy, but further clinical data are needed. Research on targeted and hormonal therapies is also underway, but many results are still preclinical and, most importantly, show conflicting results.[52]

A.3.6.4. Emerging Therapeutic Options for Malignant Meningiomas

Brachytherapy, already mentioned in a previous section, is a possible therapeutic option for patients with WHO grade III meningiomas in terms of improved survival. It involves the use of iodine-125 seeds which are implanted in the resection cavity. Unfortunately, high rates of serious complications (such as radiation necrosis) have also been reported.[56]

Immunotherapy, on the other hand, is still at its most rudimentary stage for meningiomas. Immune checkpoint inhibitors, such as the ones inhibiting cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death 1 (PD-1)/PD-ligand 1 (PD-L1), have already shown promising results in their use for aggressive malignancies such as metastatic melanoma. Still, before we can implement such therapies in the field of meningiomas, we must first understand the immunological expression profile of meningiomas. A study undertaken at the University of California, San Francisco found that PD-L1 is expressed by meningiomas and even more so in higher grade tumors, and was simultaneously a marker of worse overall survival.[57] That being said, we may one day see the use of PD-1/ PD-L1 checkpoint inhibitors in clinical use for patients with higher grade meningiomas.

A.3.7. Prognosis of WHO Grade III Meningioma Patients

A.3.7.1. Previous Studies on WHO Grade III Meningiomas

Tables 5 and 6 aggregate a large number of past studies on WHO grade III meningiomas following a wide search of the PubMed/MEDLINE® database.

In this list, studies which only focused on specific treatments (e.g., radiotherapy) were not included, seeing that the focus of this review was on patients treated primarily with surgery. We also excluded case reports of single patients or series where only one WHO grade III meningioma was present.

A case series of 6 cases of anaplastic meningioma was also published in 2018 but offered no information on the survival of these patients, and hence was excluded as well.[58] Other studies chose to aggregate data from patients with “atypical and anaplastic” (presumably, referring to WHO grade II and grade III) meningiomas, precluding the comparison of their data with studies on grade III meningiomas and thus being irrelevant for this review.[59-61] Moreover, some studies present case series based on particular characteristics of these tumors, such as the presence of metastases[48], or only present survival data for recurrent tumors[62], meaning that their cases were not representative of overall grade III meningioma demographics, and hence these studies were not included. Also excluded were studies focusing only on meningiomas present in specific intracranial locations and where not all meningiomas were WHO grade III.[63-65] There are also articles that present insufficient or no information on survival times for WHO grade III meningiomas and are thus not mentioned in tables 5 or 6.[66-69]

A broad systematic review and meta-analysis in the field of WHO grade III meningiomas seems to be lacking. We are only aware of one small systematic review of WHO grade III meningiomas, specifically of the papillary subtype.[70]

A.3.7.2. Prognostic Factors in WHO Grade III Meningiomas

Of the studies published within the last decade, median overall survival for WHO grade III meningiomas ranged from 2.6 years (Peyre et al)[71] to 5.83 years (Zhu et al)[72]. The largest clinical study to date (including data from 178 patients) reported a median overall survival of 2.9 years, and overall survival rates at 1, 5 and 10 years of 77.7%, 40% and 27.9%, respectively.[73]

In the latter study, Champeaux et al. also showed evidence that age of less than 65 years at malignant meningioma surgery, better extent of resection and adjuvant radiotherapy were all independent prognostic factors for improved survival. Previous history of WHO grade I-II meningioma, however, was associated with shorter survival in WHO grade III meningioma patients.[73]

Although still almost universally used nowadays, the relevance of the Simpson grading system as a prognostic factor has been questioned. For instance, Kuroi et al. reported that, although skull base meningiomas were more frequently incompletely resected, their prognosis was not different from that of non-skull base meningiomas owing to the fact that skull base meningiomas were more likely to be benign.[29]

As mentioned previously, there is a pressing need to increase the knowledge on these rare but extremely aggressive tumors, and randomized clinical trials are still lacking.

Table 5 – Previous studies on survival time for patients with intracranial grade III meningiomas.

Authors	Year of publication	Countries	Histologic subtypes				Total number of cases (Grade III) and comments	Overall survival (OS)
			Anaplastic	Papillary	Rhabdoid	Subtype not *clearly* specified		
Champeaux et al.[73]	2019	France & United Kingdom				178	178	2.9 yrs (median)
Masalha et al.[74]	2019	Germany				29	29 (although "anaplastic" was used to refer to these tumors, it seemed to be used as an exactly synonymous term with WHO grade III meningiomas, irrespective of subtype)	1-yr OS: 62.5% (surgery) and 71% (surgery+RT)
Maier et al.[75]	2019	Denmark	16	4	4		24	3.88 yrs (median)
Brodbelt et al.[76]	2019	United Kingdom				186	186 (population based study)	5-yr OS: 30% 10-yr OS: 15%
Holleczek et al.[77]	2019	Germany	22				22 (population based study)	4.08 yrs (median)
Peyre et al.[71]	2018	France	57				57	2.6 yrs (median)
Zhang et al.[78]	2018	China		12	11		23	4.07 yrs (mean)
Zhang et al.[79]	2018	China	56				56	3.88 yrs (mean)

Orton et al.[80]	2018	USA					755 (population based study)	5-yr OS: 41.4%
Araújo Pereira et al.[81]	2018	Brazil				4	4 (grade III)	0.8 yrs
Balasubramanian et al.[18]	2017	USA	17		1		18	4.65 yrs (median)
Sumner et al.[82]	2017	USA		190			190 (National Cancer Database study)	5-yr OS: 78.5% (surgery + RT); 62.5% (surgery alone)
Shan, Zhang, Song et al.[83]	2017	China				42	42	"Recurrent" tumors: 1-yr OS: 66.2% 3-yr OS: 39.7% 5-yr OS: 35.8%
Kim et al.[84]	2016	South Korea	14	3	2		14 (does not present separate survival data for rhabdoid vs. papillary (>50% than the total tumor area) meningiomas)	4.98 yrs (mean)
Wang et al.[85]	2016	Taiwan				16	Grade II + III study	6.00 yrs (median)
Aizer, Bi et al.[86]	2015	USA				64	64 (population based study; grade II+III study)	5-yr OS: 64.5% (GTR); 41.1% (STR)
Moliterno et al.[87]	2015	USA	37				37	2.7 yrs (median)
Cao et al.[88]	2015	China	43				43	4.92 yrs (median)
Zhu et al.[72]	2015	China					63	5.83 yrs (median)

Cain et al.[89]	2015	Australia					6 (grade II+III study)	1.6 yrs (median)
Pisćević et al.[90]	2015	Serbia				13	13 (grade II+III study)	4.17 yrs (median)
Lim et al.[91]	2013	South Korea	13	2			15	PFS: 35 mos (median) [OS not available]
Violaris et al.[92]	2013	Greece				16	16 (grade II + III study)	5-yr OS: 8.3%
Zhou, Xie et al.[93]	2013	China			12		12 (+systematic review)	PFS: 20.0 mos (median) [meta-analysis of 63 cases]
Wang, Chen et al.[94]	2013	China		30			30 (study focuses on papillary subtype only)	5 yr PFS: 26.9% [OS not available]
Duntze et al.[95]	2012	France				6	In Duntze et al.'s article, it is not clear whether anaplastic refers to the histologic subtype or is synonymous with grade III meningiomas as a whole, since the authors report only 6 grade III meningiomas, but 6 anaplastic, 1 rhabdoid and 1 papillary	6.10 yrs (mean)
Stessin et al.[96]	2012	USA				119	119 (SEER, grades II+III study)	5.83 yrs (surgery + RT) 3.50 yrs (surgery)
Patil et al.[97]	2011	USA	3				3	6.1 yrs (mean, calculated with given data)

Sughrue et al.[98]	2010	USA				63	63 (all patients received radiotherapy after surgery)	5-yr OS: 61%
Wu et al.[99]	2010	Taiwan			13		13	PFS: 36.1 mos (mean)
Durand et al.[100]	2009	France	30	1	2		33	5-yr OS: 44.0%
Rosenberg et al.[101]	2009	USA	13				13	3.4 yrs (median)
Yang et al.[102]	2008	South Korea	24				24	3.32 yrs (median)
Pasquier et al.[103]	2008	France, Netherlands, Spain, Italy, Switzerland, Turkey, Poland, Israel, Switzerland				37	37	5-yr OS: 60%
Bruna et al.[104]	2007	Spain	12				12	3.93 yrs (median)
Liu et al.[105]	2007	China	22				22	3.17 yrs (median)
Krayenbühl et al.[106]	2007	USA	4				4 (grade II+III study)	1.48 yrs (mean)
Gelabert-González et al.[107]	2004	Spain	2		1	3	6	2.96 yrs (mean, calculated with given data for 5 patients)
Cai et al.[108]	2001	USA	29				29	5-yr OS: 37.3%

GTR, gross total resection; mos, months; OS, overall survival; PFS, progression-free survival; RT, adjuvant radiotherapy; STR, subtotal resection; yr/s – year/s.

Notes:

- We excluded studies which predate the 2000 WHO classification of tumors of the central nervous system, as this is the oldest classification scheme that still holds enough similarities to the 2016 one. The vast majority of studies include only adult patients.
- It seems that all or almost all of the cases present in Wang, Zheng et al.'s article[109] are included in Wang, Chen et al.'s paper[94] (research groups from the same institution).
- Similarly, Champeaux's 2019 article[73] apparently includes all cases listed in two of his previous articles[110, 111]. Hence, in order to avoid duplication of results, we only include his most recent article.
- Cases reported in Zhao et al.'s paper[112] also seem to be included in Cao et al.'s one[88], seeing they are from the same hospital.

Table 6 – Some studies that present specific survival data for grade III spinal meningiomas

Authors	Year of publication	Countries	Histologic subtypes				Total number of cases (Grade III)	Overall survival (OS) [or Progression-free survival (PFS) if OS not available]
			Anaplastic	Subtype not *clearly* specified	Papillary	Rhabdoid		
Han et al.[113]	2020	China	4		1		5	PFS: 53.7 mos (mean)
Wright et al.[114]	2019	USA		76			76 (population-based study)	50-mos OS: 56.9%
Ye, Lv, Qian et al. [115]	2016	China	2		3		5	5-yr OS: 20%

Mos, months; OS, overall survival; PFS, progression-free survival; RT, adjuvant radiotherapy; STR, subtotal resection; yr/s – year/s.

A.4. Conclusion

Despite recent efforts on trying to reduce mortality and morbidity for WHO grade III meningioma patients, much remains to be known about their exact clinical behavior and how to optimize therapy for these patients. Table 7 reflects a personal view on some of the topics that may prove future avenues of clinical research in this area.

Table 7 – Open questions in WHO grade III meningiomas

- Cancer stem cells – tissue "screening" for prognosis and targeting CSCs for therapeutic purposes
    - In the future, could removed tissue be screened for cancer stem cell markers, in order to predict its recurrence?
- Simpson grading – is there room for improvement in order to achieve better correlation with survival?
- Surveillance in WHO grade III meningiomas – what should be the frequency of repeated MRI screening for these patients?
- Screening protocol for metastases in WHO grade III meningiomas – is it worthwhile?
- Immunotherapy for WHO grade III meningiomas

Several objectives must be set. One of them is to gather as much information as possible on the clinical outcome of WHO grade III meningiomas, preferably involving multicenter studies so as to encompass the maximum number of patients possible. Also, new treatment modalities for these tumors – possibly based on immunotherapy – must be thoroughly investigated. Finally, while no definite conclusions on the optimal therapy for these patients are reached, the neurosurgical and radio-oncological community must find ways to reduce the morbidity and psychological impact associated with both this disease and the side effects that current management protocols represent.

Only by concentrating efforts in this research field can we expect to stay true to the expression doctors so frequently use when talking to their patients and their patients' families: "we are doing everything we can".

A.5. References

1. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. Neuro Oncol. 2019;21(Supplement_5):v1-v100.
2. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, (eds.). WHO Classification of Tumours of the Central Nervous System. Revised 4th ed. Lyon, France: IARC; 2016.
3. Cushing H. The meningiomas (dural endotheliomas): their source, and favoured seats of origin. Brain. 1922;45(2):282-316.
4. al-Rodhan NR, Laws ER. Meningioma: a historical study of the tumor and its surgical management. Neurosurgery. 1990;26(5):832-46; discussion 46-7.
5. Platter F. Observationum in hominis affectibus plerisque, corpori et animo, functionum laesione, dolore, aliave molestia et vitio incommodantibus, libri tres. Basilea1614.
6. Perry A. 13 - Meningiomas. In: Perry A, Brat DJ, editors. Practical Surgical Neuropathology: A Diagnostic Approach. Second ed: Elsevier; 2018. p. 259-98.
7. Kleihues P, Burger PC, Scheithauer BW. Histological Typing of Tumours of the Central Nervous System. Second ed. Berlin, Heidelberg: Springer Berlin Heidelberg; 1993.
8. Zülch KJ. Histological typing of tumours of the central nervous system. Geneva: World Health Organization; 1979. 66 p.
9. Kleihues P, Cavenee WK. World Health Organisation classification of tumours: Pathology and genetics of tumours of the nervous system. Lyon: IARC Press; 2000.
10. Kleihues P, Louis DN, Scheithauer BW, Rorke LB, Reifenberger G, Burger PC, et al. The WHO classification of tumors of the nervous system. J Neuropathol Exp Neurol. 2002;61(3):215-25; discussion 26-9.
11. Scheithauer BW. Development of the WHO classification of tumors of the central nervous system: a historical perspective. Brain Pathol. 2009;19(4):551-64.
12. Louis DN, Ohgaki H, Wiestler OD, Cavanee WK. WHO Classification of Tumours of the Central Nervous System. Lyon: IARC; 2007.
13. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007;114(2):97-109.
14. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131(6):803-20.
15. Combs SE, Schulz-Ertner D, Debus J, von Deimling A, Hartmann C. Improved correlation of the neuropathologic classification according to adapted world health organization

classification and outcome after radiotherapy in patients with atypical and anaplastic meningiomas. Int J Radiat Oncol Biol Phys. 2011;81(5):1415-21.

16. Perry A, Scheithauer BW, Stafford SL, Lohse CM, Wollan PC. "Malignancy" in meningiomas: a clinicopathologic study of 116 patients, with grading implications. Cancer. 1999;85(9):2046-56.

17. IARC. WHO Classification of Tumours Editorial Board meeting: Central Nervous System Tumours and Paediatric Tumours, 5th edition 2020 [Available from: https://www.iarc.fr/news-events/who-classification-of-tumours-editorial-board-meeting-central-nervous-system-tumours-and-paediatric-tumours-5th-edition/.

18. Balasubramanian SK, Sharma M, Silva D, Karivedu V, Schmitt P, Stevens GH, et al. Longitudinal experience with WHO Grade III (anaplastic) meningiomas at a single institution. J Neurooncol. 2017;131(3):555-63.

19. Fan MC, Zhang X, Wang QL, Cheng L, Dai CY, Yu D, et al. Malignant meningioma of the cerebellopontine angle in a 2-year-old girl: a case report and literature review. Chin J Cancer. 2013;32(7):415-7.

20. Bayram I, Kiymaz N, Harman M, Uğra S. Malignant meningioma in a 3-year-old girl. Am J Clin Oncol. 2006;29(3):320-1.

21. Kshettry VR, Ostrom QT, Kruchko C, Al-Mefty O, Barnett GH, Barnholtz-Sloan JS. Descriptive epidemiology of World Health Organization grades II and III intracranial meningiomas in the United States. Neuro Oncol. 2015;17(8):1166-73.

22. Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. J Neurooncol. 2010;99(3):307-14.

23. Bi WL, Zhang M, Wu WW, Mei Y, Dunn IF. Meningioma Genomics: Diagnostic, Prognostic, and Therapeutic Applications. Front Surg. 2016;3:40.

24. Quddusi A, Shamim MS, Virani Q. Effect of pregnancy on growth of intracranial meningiomas. J Pak Med Assoc. 2019;69(7):1057-8.

25. Lusis EA, Scheithauer BW, Yachnis AT, Fischer BR, Chicoine MR, Paulus W, et al. Meningiomas in pregnancy: a clinicopathologic study of 17 cases. Neurosurgery. 2012;71(5):951-61.

26. Tamura Y, Miyatake S, Nonoguchi N, Miyata S, Yokoyama K, Doi A, et al. Boron neutron capture therapy for recurrent malignant meningioma. Case report. J Neurosurg. 2006;105(6):898-903.

27. Metellus P, Nanni I, Dussert C, Trinkhaus M, Fuentes S, Chinot O, et al. [Prognostic implications of biologic markers in intracranial meningiomas: 120 cases]. Neurochirurgie. 2008;54(6):750-6.

28. Pravdenkova S, Al-Mefty O, Sawyer J, Husain M. Progesterone and estrogen receptors: opposing prognostic indicators in meningiomas. J Neurosurg. 2006;105(2):163-73.

29. Kuroi Y, Matsumoto K, Shibuya M, Kasuya H. Progesterone Receptor Is Responsible for Benign Biology of Skull Base Meningioma. World Neurosurg. 2018;118:e918-e24.
30. Hua L, Zhu H, Li J, Tang H, Kuang D, Wang Y, et al. Prognostic value of estrogen receptor in WHO Grade III meningioma: a long-term follow-up study from a single institution. J Neurosurg. 2018;128(6):1698-706.
31. Fewings PE, Battersby RD, Timperley WR. Long-term follow up of progesterone receptor status in benign meningioma: a prognostic indicator of recurrence? J Neurosurg. 2000;92(3):401-5.
32. Cornelius JF, Slotty PJ, Steiger HJ, Hänggi D, Polivka M, George B. Malignant potential of skull base versus non-skull base meningiomas: clinical series of 1,663 cases. Acta Neurochir (Wien). 2013;155(3):407-13.
33. Sade B, Chahlavi A, Krishnaney A, Nagel S, Choi E, Lee JH. World Health Organization Grades II and III meningiomas are rare in the cranial base and spine. Neurosurgery. 2007;61(6):1194-8; discussion 8.
34. Balducci L, Ershler WB. Cancer and ageing: a nexus at several levels. Nat Rev Cancer. 2005;5(8):655-62.
35. Baldi I, Engelhardt J, Bonnet C, Bauchet L, Berteaud E, Grüber A, et al. Epidemiology of meningiomas. Neurochirurgie. 2018;64(1):5-14.
36. Park JS, Sade B, Oya S, Kim CG, Lee JH. The influence of age on the histological grading of meningiomas. Neurosurg Rev. 2014;37(3):425-9; discussion 429.
37. Amano T, Nakamizo A, Michiwaki Y, Matsuo S, Fujioka Y, Nagata S. Surgical outcome in elderly patients with intracranial meningioma. J Clin Neurosci. 2018;56:63-6.
38. Pamir MN, Black PM, Fahlbusch R. Meningiomas: A Comprehensive Text. Philadelphia: Saunders/Elsevier; 2010.
39. Pavelka M, Roth J. Junctional Complex. Functional Ultrastructure: Atlas of Tissue Biology and Pathology. Vienna: Springer Vienna; 2010. p. 166-7.
40. Cimino PJ, Yoda RA, Wirsching HG, Warrick JI, Dorschner MO, Ferreira M. Genomic profiling of anaplastic meningioma identifies recurrent genetic alterations with relevance to lower-grade meningioma. Neuropathol Appl Neurobiol. 2019;45(2):179-82.
41. Theeler BJ. De novo and secondary anaplastic meningiomas: natural history, prognosis, and the TERT promoter. Neuro Oncol. 2018;20(8):1009-10.
42. Clarke MF. Clinical and Therapeutic Implications of Cancer Stem Cells. N Engl J Med. 2019;380(23):2237-45.
43. Shivapathasundram G, Wickremesekera AC, Tan ST, Itinteang T. Tumour stem cells in meningioma: A review. J Clin Neurosci. 2018;47:66-71.

44. Ongaratti BR, Silva CB, Trott G, Haag T, Leães CG, Ferreira NP, et al. Expression of merlin, NDRG2, ERBB2, and c-MYC in meningiomas: relationship with tumor grade and recurrence. Braz J Med Biol Res. 2016;49(4):e5125.
45. Freitag D, McLean AL, Simon M, Koch A, Grube S, Walter J, et al. NANOG overexpression and its correlation with stem cell and differentiation markers in meningiomas of different WHO grades. Mol Carcinog. 2017;56(8):1953-64.
46. Tang H, Zhu H, Wang X, Hua L, Li J, Xie Q, et al. KLF4 is a tumor suppressor in anaplastic meningioma stem-like cells and human meningiomas. J Mol Cell Biol. 2017;9(4):315-24.
47. Surov A, Gottschling S, Bolz J, Kornhuber M, Alfieri A, Holzhausen HJ, et al. Distant metastases in meningioma: an underestimated problem. J Neurooncol. 2013;112(3):323-7.
48. Kessler RA, Garzon-Muvdi T, Yang W, Weingart J, Olivi A, Huang J, et al. Metastatic Atypical and Anaplastic Meningioma: A Case Series and Review of the Literature. World Neurosurg. 2017;101:47-56.
49. Magu SK, Gupta MK, Behl A. Malignant Meningioma - Clinicopathological Study of an Unusual Presentation of a Rare Malignancy. Med J Armed Forces India. 2003;59(2):166-8.
50. Beutler BD, Nguyen ET, Parker RA, Tran C, Acharya J, Torres FA, et al. Metastatic meningioma: Case report of a WHO grade I meningioma with liver metastases and review of the literature. Radiol Case Rep. 2020;15(2):110-6.
51. Golemi A, Ambrosini A, Cecchi P, Ruiu A, Chondrogiannis S, Farsad M, et al. (68)Ga-DOTANOC PET/CT detection of multiple extracranial localizations in a patient with anaplastic meningioma. Rev Esp Med Nucl Imagen Mol. 2015;34(4):258-60.
52. Cossu G, Messerer M, Parker F, Levivier M, Daniel RT. Meningiomas' Management: An Update of the Literature. In: Agrawal A, editor. Neurooncology - Newer Developments: IntechOpen; 2016. p. 361-79.
53. Simpson D. The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry. 1957;20(1):22-39.
54. Borovich B, Doron Y, Braun J, Guilburd JN, Zaaroor M, Goldsher D, et al. Recurrence of intracranial meningiomas: the role played by regional multicentricity. Part 2: Clinical and radiological aspects. J Neurosurg. 1986;65(2):168-71.
55. Kinjo T, al-Mefty O, Kanaan I. Grade zero removal of supratentorial convexity meningiomas. Neurosurgery. 1993;33(3):394-9; discussion 9.
56. Walcott BP, Nahed BV, Brastianos PK, Loeffler JS. Radiation Treatment for WHO Grade II and III Meningiomas. Front Oncol. 2013;3:227.
57. Han SJ, Reis G, Kohanbash G, Shrivastav S, Magill ST, Molinaro AM, et al. Expression and prognostic impact of immune modulatory molecule PD-L1 in meningioma. J Neurooncol. 2016;130(3):543-52.

58. Cao H, Jiang B, Zhao Y, Fan C. A rare subtype of meningioma: Case series of anaplastic meningioma and review of the literature. Medicine (Baltimore). 2018;97(23):e11019.
59. Garzon-Muvdi T, Yang W, Lim M, Brem H, Huang J. Atypical and anaplastic meningioma: outcomes in a population based study. J Neurooncol. 2017;133(2):321-30.
60. Vranic A, Popovic M, Cör A, Prestor B, Pizem J. Mitotic count, brain invasion, and location are independent predictors of recurrence-free survival in primary atypical and malignant meningiomas: a study of 86 patients. Neurosurgery. 2010;67(4):1124-32.
61. Chohan MO, Ryan CT, Singh R, Lanning RM, Reiner AS, Rosenblum MK, et al. Predictors of Treatment Response and Survival Outcomes in Meningioma Recurrence with Atypical or Anaplastic Histology. Neurosurgery. 2018;82(6):824-32.
62. Ko KW, Nam DH, Kong DS, Lee JI, Park K, Kim JH. Relationship between malignant subtypes of meningioma and clinical outcome. J Clin Neurosci. 2007;14(8):747-53.
63. Belinsky I, Murchison AP, Evans JJ, Andrews DW, Farrell CJ, Casey JP, et al. Spheno-Orbital Meningiomas: An Analysis Based on World Health Organization Classification and Ki-67 Proliferative Index. Ophthalmic Plast Reconstr Surg. 2018;34(2):143-50.
64. Qiao L, Yu C, Zhang H, Zhang M, Qu Y, Ren M, et al. Clinical outcomes and survival analysis for petroclival meningioma patients receiving surgical resection: an analysis of 176 cases. Cancer Manag Res. 2019;11:5949-59.
65. Jiang Y, Lv L, Li J, Ma W, Chen C, Zhou P, et al. Clinical features, radiological findings, and treatment outcomes of high-grade lateral ventricular meningiomas: a report of 26 cases. Neurosurg Rev. 2019.
66. Li D, Jiang P, Xu S, Li C, Xi S, Zhang J, et al. Survival impacts of extent of resection and adjuvant radiotherapy for the modern management of high-grade meningiomas. J Neurooncol. 2019;145(1):125-34.
67. Bozkurt SU, Ayan E, Bolukbasi F, Elmaci I, Pamir N, Sav A. Immunohistochemical expression of SPARC is correlated with recurrence, survival and malignant potential in meningiomas. APMIS. 2009;117(9):651-9.
68. Engenhart-Cabillic R, Farhoud A, Sure U, Heinze S, Henzel M, Mennel HD, et al. Clinicopathologic features of aggressive meningioma emphasizing the role of radiotherapy in treatment. Strahlenther Onkol. 2006;182(11):641-6.
69. Bhat AR, Wani MA, Kirmani AR, Ramzan AU. Histological-subtypes and anatomical location correlated in meningeal brain tumors (meningiomas). J Neurosci Rural Pract. 2014;5(3):244-9.
70. Fong C, Nagasawa DT, Chung LK, Voth B, Cremer N, Thill K, et al. Systematic Analysis of Outcomes for Surgical Resection and Radiotherapy in Patients with Papillary Meningioma. J Neurol Surg B Skull Base. 2015;76(4):252-6.

71. Peyre M, Gauchotte G, Giry M, Froehlich S, Pallud J, Graillon T, et al. De novo and secondary anaplastic meningiomas: a study of clinical and histomolecular prognostic factors. Neuro Oncol. 2018;20(8):1113-21.
72. Zhu H, Xie Q, Zhou Y, Chen H, Mao Y, Zhong P, et al. Analysis of prognostic factors and treatment of anaplastic meningioma in China. J Clin Neurosci. 2015;22(4):690-5.
73. Champeaux C, Jecko V, Houston D, Thorne L, Dunn L, Fersht N, et al. Malignant Meningioma: An International Multicentre Retrospective Study. Neurosurgery. 2019;85(3):E461-E9.
74. Masalha W, Heiland DH, Delev D, Fennell JT, Franco P, Scheiwe C, et al. Survival and Prognostic Predictors of Anaplastic Meningiomas. World Neurosurg. 2019;131:e321-e8.
75. Maier AD, Bartek J, Eriksson F, Ugleholdt H, Juhler M, Broholm H, et al. Clinical and histopathological predictors of outcome in malignant meningioma. Neurosurg Rev. 2019.
76. Brodbelt AR, Barclay ME, Greenberg D, Williams M, Jenkinson MD, Karabatsou K. The outcome of patients with surgically treated meningioma in England: 1999-2013. A cancer registry data analysis. Br J Neurosurg. 2019;33(6):641-7.
77. Holleczek B, Zampella D, Urbschat S, Sahm F, von Deimling A, Oertel J, et al. Incidence, mortality and outcome of meningiomas: A population-based study from Germany. Cancer Epidemiol. 2019;62:101562.
78. Zhang GJ, Zhang GB, Zhang YS, Li H, Li CB, Zhang LW, et al. World Health Organization Grade III (Nonanaplastic) Meningioma: Experience in a Series of 23 Cases. World Neurosurg. 2018;112:e754-e62.
79. Zhang GJ, Zhang YS, Zhang GB, Li D, Zhang LW, Wu Z, et al. Prognostic factors and the management of anaplastic meningioma. Clin Neurol Neurosurg. 2018;170:13-9.
80. Orton A, Frandsen J, Jensen R, Shrieve DC, Suneja G. Anaplastic meningioma: an analysis of the National Cancer Database from 2004 to 2012. J Neurosurg. 2018;128(6):1684-9.
81. Pereira BJA, de Almeida AN, de Aguiar PHP, Paiva WS, Cabrera HN, da Silva CC, et al. Atypical and Malignant Meningiomas: Neurooncologic Management in a Brazilian cohort. World Neurosurg. 2018;110:e20-e3.
82. Sumner WA, Amini A, Hankinson TC, Foreman NK, Gaspar LE, Kavanagh BD, et al. Survival benefit of postoperative radiation in papillary meningioma: Analysis of the National Cancer Data Base. Rep Pract Oncol Radiother. 2017;22(6):495-501.
83. Shan B, Zhang J, Song Y, Xu J. Prognostic factors for patients with World Health Organization grade III meningiomas treated at a single center. Medicine (Baltimore). 2017;96(26):e7385.

84. Kim JK, Jung TY, Jung S, Lee KH, Kim SK, Lee EJ. Meningiomas with Rhabdoid or Papillary Components : Prognosis and Comparison with Anaplastic Meningiomas. J Korean Neurosurg Soc. 2016;59(4):357-62.
85. Wang YC, Chuang CC, Wei KC, Chang CN, Lee ST, Wu CT, et al. Long Term Surgical Outcome and Prognostic Factors of Atypical and Malignant Meningiomas. Sci Rep. 2016;6:35743.
86. Aizer AA, Bi WL, Kandola MS, Lee EQ, Nayak L, Rinne ML, et al. Extent of resection and overall survival for patients with atypical and malignant meningioma. Cancer. 2015;121(24):4376-81.
87. Moliterno J, Cope WP, Vartanian ED, Reiner AS, Kellen R, Ogilvie SQ, et al. Survival in patients treated for anaplastic meningioma. J Neurosurg. 2015;123(1):23-30.
88. Cao X, Hao S, Wu Z, Wang L, Jia G, Zhang L, et al. Survival rates, prognostic factors and treatment of anaplastic meningiomas. J Clin Neurosci. 2015;22(5):828-33.
89. Cain SA, Smoll NR, Van Heerden J, Tsui A, Drummond KJ. Atypical and malignant meningiomas: Considerations for treatment and efficacy of radiotherapy. J Clin Neurosci. 2015;22(11):1742-8.
90. Pisćević I, Villa A, Milićević M, Ilić R, Nikitović M, Cavallo LM, et al. The Influence of Adjuvant Radiotherapy in Atypical and Anaplastic Meningiomas: A Series of 88 Patients in a Single Institution. World Neurosurg. 2015;83(6):987-95.
91. Lim YS, Kim MK, Park BJ, Kim TS, Lim YJ. Long term clinical outcomes of malignant meningiomas. Brain Tumor Res Treat. 2013;1(2):85-90.
92. Violaris K, Katsarides V, Karakyriou M, Sakellariou P. Surgical Outcome of Treating Grades II and III Meningiomas: A Report of 32 Cases. Neurosci J. 2013;2013:706481.
93. Zhou Y, Xie Q, Gong Y, Mao Y, Zhong P, Che X, et al. Clinicopathological analysis of rhabdoid meningiomas: report of 12 cases and a systematic review of the literature. World Neurosurg. 2013;79(5-6):724-32.
94. Wang XQ, Chen H, Zhao L, Li ST, Hu J, Mei GH, et al. Intracranial papillary meningioma: a clinicopathologic study of 30 cases at a single institution. Neurosurgery. 2013;73(5):777-90; discussion 89.
95. Duntze J, Metellus P, Litre CF, Eap C, Theret E, Colin P, et al. [Management of WHO grade II and II meningiomas: retrospective study of surgical series of 36 cases at a single institution]. Neurochirurgie. 2012;58(5):275-81.
96. Stessin AM, Schwartz A, Judanin G, Pannullo SC, Boockvar JA, Schwartz TH, et al. Does adjuvant external-beam radiotherapy improve outcomes for nonbenign meningiomas? A Surveillance, Epidemiology, and End Results (SEER)-based analysis. J Neurosurg. 2012;117(4):669-75.

97. Patil S, Scheithauer BW, Strom RG, Mafra M, Chicoine MR, Perry A. Malignant meningiomas with epithelial (adenocarcinoma-like) metaplasia: a study of 3 cases. Neurosurgery. 2011;69(4):884-92.
98. Sughrue ME, Sanai N, Shangari G, Parsa AT, Berger MS, McDermott MW. Outcome and survival following primary and repeat surgery for World Health Organization Grade III meningiomas. J Neurosurg. 2010;113(2):202-9.
99. Wu YT, Lin JW, Wang HC, Lee TC, Ho JT, Lin YJ. Clinicopathologic analysis of rhabdoid meningioma. J Clin Neurosci. 2010;17(10):1271-5.
100. Durand A, Labrousse F, Jouvet A, Bauchet L, Kalamaridès M, Menei P, et al. WHO grade II and III meningiomas: a study of prognostic factors. J Neurooncol. 2009;95(3):367-75.
101. Rosenberg LA, Prayson RA, Lee J, Reddy C, Chao ST, Barnett GH, et al. Long-term experience with World Health Organization grade III (malignant) meningiomas at a single institution. Int J Radiat Oncol Biol Phys. 2009;74(2):427-32.
102. Yang SY, Park CK, Park SH, Kim DG, Chung YS, Jung HW. Atypical and anaplastic meningiomas: prognostic implications of clinicopathological features. J Neurol Neurosurg Psychiatry. 2008;79(5):574-80.
103. Pasquier D, Bijmolt S, Veninga T, Rezvoy N, Villa S, Krengli M, et al. Atypical and malignant meningioma: outcome and prognostic factors in 119 irradiated patients. A multicenter, retrospective study of the Rare Cancer Network. Int J Radiat Oncol Biol Phys. 2008;71(5):1388-93.
104. Bruna J, Brell M, Ferrer I, Gimenez-Bonafe P, Tortosa A. Ki-67 proliferative index predicts clinical outcome in patients with atypical or anaplastic meningioma. Neuropathology. 2007;27(2):114-20.
105. Liu Y, Liu M, Li F, Wu C, Zhu S. Malignant meningiomas: a retrospective study of 22 cases. Bull Cancer. 2007;94(10):E27-31.
106. Krayenbühl N, Pravdenkova S, Al-Mefty O. De novo versus transformed atypical and anaplastic meningiomas: comparisons of clinical course, cytogenetics, cytokinetics, and outcome. Neurosurgery. 2007;61(3):495-503; discussion 503-4.
107. Gelabert-González M, Fernández-Villa JM, Iglesias-Pais M. [Atypical and malignant intracranial meningiomas]. Rev Neurol. 2004;38(4):304-10.
108. Cai DX, Banerjee R, Scheithauer BW, Lohse CM, Kleinschmidt-Demasters BK, Perry A. Chromosome 1p and 14q FISH analysis in clinicopathologic subsets of meningioma: diagnostic and prognostic implications. J Neuropathol Exp Neurol. 2001;60(6):628-36.
109. Wang DJ, Zheng MZ, Gong Y, Xie Q, Wang Y, Cheng HX, et al. Papillary meningioma: clinical and histopathological observations. Int J Clin Exp Pathol. 2013;6(5):878-88.

110. Champeaux C, Wilson E, Brandner S, Shieff C, Thorne L. World Health Organization grade III meningiomas. A retrospective study for outcome and prognostic factors assessment. Br J Neurosurg. 2015;29(5):693-8.
111. Champeaux C, Jecko V. World Health Organization grade III meningiomas. A retrospective study for outcome and prognostic factors assessment. Neurochirurgie. 2016;62(4):203-8.
112. Zhao P, Hu M, Zhao M, Ren X, Jiang Z. Prognostic factors for patients with atypical or malignant meningiomas treated at a single center. Neurosurg Rev. 2015;38(1):101-7; discussion 7.
113. Han B, Zhang L, Jia W, Yang J. Clinical features and surgical outcomes of high-grade spinal meningiomas: Report of 19 cases and literature review. J Clin Neurosci. 2020;72:264-9.
114. Wright JM, Wright CH, Cioffi G, Raghavan A, Hdeib A, Kasliwal MK, et al. Survival in Patients with High-Grade Spinal Meningioma: An Analysis of the National Cancer Database. World Neurosurg. 2019;129:e749-e53.
115. Ye J, Lv G, Qian J, Zhu J, Han R, Luo C. Clinical features and prognostic factors of WHO II and III adult spinal meningiomas: analysis of 25 cases in a single center. J Neurooncol. 2016;128(2):349-56.

Part B. World Health Organization Grade III Meningiomas: A Retrospective Study at an Academic Medical Center

Title:

World Health Organization Grade III Meningiomas: A Retrospective Study at an Academic Medical Center

Author names and affiliations:

Eduarda Sá-Marta[a]; José Luís Alves[a, b]; Marcos Barbosa[a, b, c, d]

a – Faculty of Medicine, University of Coimbra, Coimbra, Portugal
b – Department of Neurosurgery, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
c – Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal
d – Clinical Academic Center of Coimbra (CACC), Coimbra, Portugal.

Corresponding author:

Eduarda Sá-Marta
Faculty of Medicine, University of Coimbra, Coimbra, Portugal.
Polo III – Polo das Ciências da Saúde
Azinhaga de Santa Comba, Celas
3000-548 Coimbra
Portugal
Electronic address: eduardasamarta@gmail.com

Highest academic degrees for all authors: Eduarda Sá-Marta, BS; José Luís Alves, MD; Marcos Barbosa, MD, PhD

Key words: Anaplastic meningioma; Malignant meningioma; Papillary meningioma; Prognosis; Radiotherapy; Rhabdoid meningioma; WHO grade III meningioma

Short title: WHO Grade III Meningiomas

Abbreviations and Acronyms

CBTRUS: Central Brain Tumor Registry of the United States

CHUC: Centro Hospitalar e Universitário de Coimbra (Coimbra University Hospital Center)

CI: Confidence interval

CSF: Cerebrospinal fluid

CT: Computed tomography

EBRT: External beam radiation therapy

GTR: Gross total resection (or gross totally resected)

HR: Hazard ratio

KFS: Karnofsky Performance Status

MRI: Magnetic resonance imaging

OS: Overall survival

PFS: Progression-free survival

RT: Radiotherapy

SD: Standard deviation

SRS: Stereotactic radiosurgery

STR: Subtotal resection (or subtotally resected)

WHO: World Health Organization

Abstract

Background:

Meningiomas are the most common primary brain tumors and are generally considered to be benign. However, a very rare subgroup of meningiomas, classified as World Health Organization (WHO) Grade III meningiomas, can display extremely aggressive behavior and high rates of recurrence. Despite ongoing research, data on the clinical outcome of this subgroup of meningiomas are still limited.

Methods:

Medical records of patients with intracranial WHO grade III meningiomas diagnosed between 2000 and 2018 at the Coimbra University Hospital Center were retrospectively reviewed and several variables of interest and their relation to patients' survival were analyzed. Due to its extreme rarity, a detailed description of the only rhabdoid meningioma in our series was also included.

Results:

Of the 26 patients included in the final analysis, 23 had anaplastic meningiomas, 2 had papillary meningiomas, and 1 had a rhabdoid meningioma. Median overall survival and median progression free survival were 2.45 and 1.22 years, respectively. Overall survival rates at 1, 2 and 5 years were 73%, 57% and 35%, respectively. Adjuvant radiotherapy correlated with improved survival for subtotally resected meningiomas, but not for gross totally resected meningiomas. There was a trend toward improved overall survival with gross total resection versus subtotal resection, but this difference failed to reach statistical significance.

Conclusions:

WHO Grade III meningiomas portend a devastating prognosis and the impact of extent of resection and adjuvant therapies still needs further clarification. We thus hope to have contributed to the bulk of knowledge concerning the clinical outcome of these meningiomas.

Introduction

Meningiomas are the most common primary brain tumors (37.6% of all central nervous system tumors), according to recent data from the Central Brain Tumor Registry of the United States (CBTRUS).[1] Meningiomas are thought to arise from arachnoid cap cells. The vast majority of meningiomas are considered to be benign tumors (World Health Organization [WHO] grade I).[2] However, around 20% of meningiomas display aggressive behavior and have higher rates of recurrence. These meningiomas are classified as WHO grade II or grade III meningiomas, the latter being the most aggressive type.[2] Representing 1.7% of all the meningiomas with documented WHO grade in the United States[1], grade III meningiomas are associated with a much worse prognosis.

Anaplastic (malignant), papillary and rhabdoid meningiomas all correspond to WHO grade III meningiomas.[2] Although some interpret WHO grade III meningiomas as being synonymous with anaplastic and malignant meningiomas, this seems to generate ambiguity by not making clear which exact histologic subtypes studies on WHO grade III meningiomas encompass.

In our study, we chose to include all of the histologic subtypes of grade III meningiomas histology as defined by the 2016 WHO Classification of Tumors of the Central Nervous System (4th revised edition).[2] The term “grade III meningiomas” in our article thus refers to the WHO classification scheme.

Despite the increasing number of case series of WHO grade III meningiomas, more substantial evidence is needed to support the types of treatment, besides surgery, that many of these patients currently undergo (e.g., radiotherapy and sometimes chemotherapy). Also, there are obvious discrepancies in the literature regarding what is indeed the overall survival (ranging from a median of 2.6 years[3] to a median of 5.83 years[4] in recent studies) for these patients.

We thus set out to investigate the clinical, pathological, radiological characteristics of WHO grade III meningioma patients and their clinical outcome at our institution. Our objective was not only to ascertain their overall and progression-free survival, but also to find possible prognostic factors for these patients.

Methods

Study Design and Definitions

A search of the neuropathology database at Coimbra University Hospital Center/Centro Hospitalar e Universitário de Coimbra (CHUC) was done using the terms “anaplastic meningioma”, “papillary meningioma” and “rhabdoid meningioma”. All pathology reports since January 2000 relating to a grade III diagnosis were included. Patients younger than 18 years were excluded from this study.

Some pathology reports predated the 2016 WHO Classification of Tumors of the Central Nervous System (4th revised edition), but these were reviewed in order to ensure that the meningiomas that were included in this study fulfilled the criteria for WHO grade III meningiomas according to the most recent classification.[2]

Variables that were looked at included: patient demographics (such as age, gender, symptoms, tumor location and size and, when available, Karnofsky Performance Status[5]), radiological and histopathological tumor characteristics, mode of treatment, extent of resection (Simpson grade[6]), progression-free survival rate, overall survival rate and treatment complications.

The date of diagnosis was set as the date of the surgery that lead to the histopathological diagnosis of WHO grade III meningioma (irrespective of whether the patient had had a non-grade III meningioma prior to this diagnosis). Every patient in our series received primary treatment at Centro Hospitalar e Universitário de Coimbra (CHUC). Bone invasion was verified through histopathological confirmation. Brain invasion was confirmed through histopathology as well. Venous sinus invasion was normally detected on imaging, but operative reports were also carefully examined to look for evidence of venous sinus invasion. Tumor size was retrieved from imaging reports that were done just prior to grade III resection.

In the present study, we used the term “recurrent” to refer to grade III meningiomas who later recurred, leaving the term “secondary” to refer to grade III meningiomas that occurred in patients with a previous non-grade III meningioma diagnosis. Primary (or *de novo*) meningiomas thus corresponded to WHO grade III tumors that were diagnosed in a patient with no previous history of a WHO grade I or II meningioma.

Overall survival was calculated from the date of the first surgery that led to the pathological diagnosis of a grade III meningioma to the date of death.

Progression-free survival (i.e., time until grade III recurrence) was measured from the time of surgery that led to grade III meningioma diagnosis to the date of first symptomatic relapse, detection of tumor recurrence through imaging, or death (whichever occurred first). If the precise date was not clear in the medical records, the date of surgery for recurrence was interpreted as the date of grade III recurrence. At our institution, follow-up appointments and surveillance MRIs to check for tumor recurrence were normally first done 1-3 months after initial surgery, then every 6 months in the first 2 years, then every year indefinitely.

The censoring date was February 1, 2020, thus hopefully excluding any possible deaths due to the COVID-19 pandemic (the first reported case of COVID-19 in Portugal was on March 2, 2020[7]). To ensure minimal adequate follow-up time, we only considered patients who were diagnosed before January 1, 2019 in our survival analysis.

Time to transformation from a grade I or II meningioma to a grade III (secondary) meningioma was calculated from the date of *first* meningioma diagnosis (grade I or II) to the date of grade III meningioma diagnosis.

The Simpson grade of the first WHO grade III meningioma resection was considered, irrespective of posterior resections.

The following terminology for grouping Simpson grade resections was used: Gross Total Resection (GTR) corresponded to Simpson grades I and II resections; Subtotal Resection (STR) was equivalent to a Simpson grade IV resection. Some researchers[8, 9] use the term Gross Total Resection (GTR) for Simpson grades I+II+III but, considering that we did not have any Simpson grade III removal in our series, we did not include it in our definition of GTR. We also did not have any Simpson grade V (biopsy) as first surgery for a grade III meningioma in our case series.

The degree of resection was obtained from operative reports. A post-operative computed tomography (CT) was routinely done to confirm grade of resection. Thus, if post-operative imaging revealed a residual meningioma, even if in the surgeon's view a gross total resection had been achieved, a Simpson Grade IV (subtotal resection) was considered instead.

Adjuvant radiotherapy and adjuvant chemotherapy refer to radiotherapy and chemotherapy treatments received *after* grade III diagnosis, irrespective of whether a patient had previously received radiotherapy and/or chemotherapy for a non-grade III meningioma. The radiotherapy treatments at our institution were generally conducted following the most recent guidelines of the National Comprehensive Cancer Network at the time.[10] Patients who underwent external beam radiation therapy normally received a total dose of 60 Gy in 30 fractions over 6 weeks directed at the surgical bed with a margin whenever possible. After a thorough analysis of

medical records, we could not find any indication that preoperative tumor embolization had been carried out in any of our patients.

The Karnofsky Performance Status (KPS) reported here refers to the period after surgery.

Portugal has a Death Registration System that is 100% electronic since January 2014.[11] All the patients who were electronically registered as “alive” at censoring date had their WHO grade III meningioma diagnosis after January 2014, meaning that we were able to capture both the true number of deaths and of alive patients at censoring date.

Statistical Analysis

Survival rates were graphically represented using the Kaplan-Meier method and compared between different groups using the log-rank (Mantel-Cox) test. Outcome was defined as death and as recurrence or death in the analyses for overall survival and progression-free survival, respectively. Whenever a log-rank test yielded a p-value <0.10, multivariate Cox proportional hazards regression was further used to investigate possible prognostic factors. For the Cox proportional hazards regression analysis, statistical significance was set at $p<0.05$. All p-values were two-sided. All statistical tests were carried out using the IBM SPSS Statistics software for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

Ethical Approval

This study was approved by the Institutional Review Board at the Coimbra University Hospital Center (approval 062/CES; study number CHUC-017-20) and a waiver for informed consent was obtained due to the retrospective nature of the study and the full anonymization of patients’ data. Patients less than 18 years old were also excluded. This study adheres to the tenets of the Code of Ethics of the World Medical Association (Declaration of Helsinki), revised in 2013.[12]

Results

Through our tumor database search, we were able to find a total of 32 patients diagnosed with a WHO grade III meningioma. However, we were not able to trace the medical records of 3 patients, as one of them was lost to follow-up and the medical records of the other two were physically located at Hospital Geral (Covões). We were not able to retrieve these medical records due to the fact that the latter hospital had been transformed to a COVID-only facility while this study was being carried out. Of the remaining 29 patients (26 anaplastic, 2 papillary, 1 rhabdoid), 3 had to be excluded due to insufficient follow-up time (diagnosis after February 1, 2019). We were finally left with a total of 26 patients, of which 23 (88.5%) had anaplastic meningiomas, 2 (7.7%) had papillary meningiomas, and 1 (3.8%) had a rhabdoid meningioma. A distribution of the histologic subtypes diagnosed per year at our medical center is shown in Figure 1.

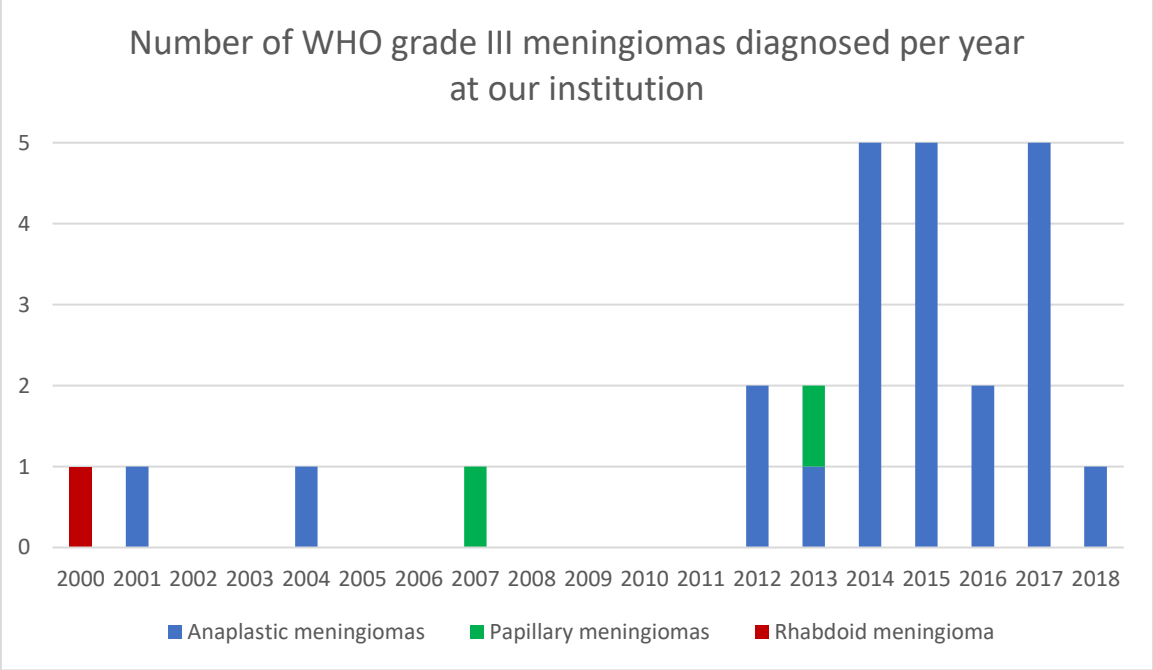


Figure 1. Number of WHO grade III meningiomas diagnosed per year at our institution (CHUC).

Additionally, we provide a diagram indicating the main treatments that patients in the present series underwent at our institution (Figure 2). We stress that patients were not randomized for this study and that the decision to undergo adjuvant radiotherapy was taken on an individual basis by the Brain Tumor Board at CHUC taking into consideration (among other factors) each patient's overall health status and the available therapeutic modalities at the time of diagnosis.

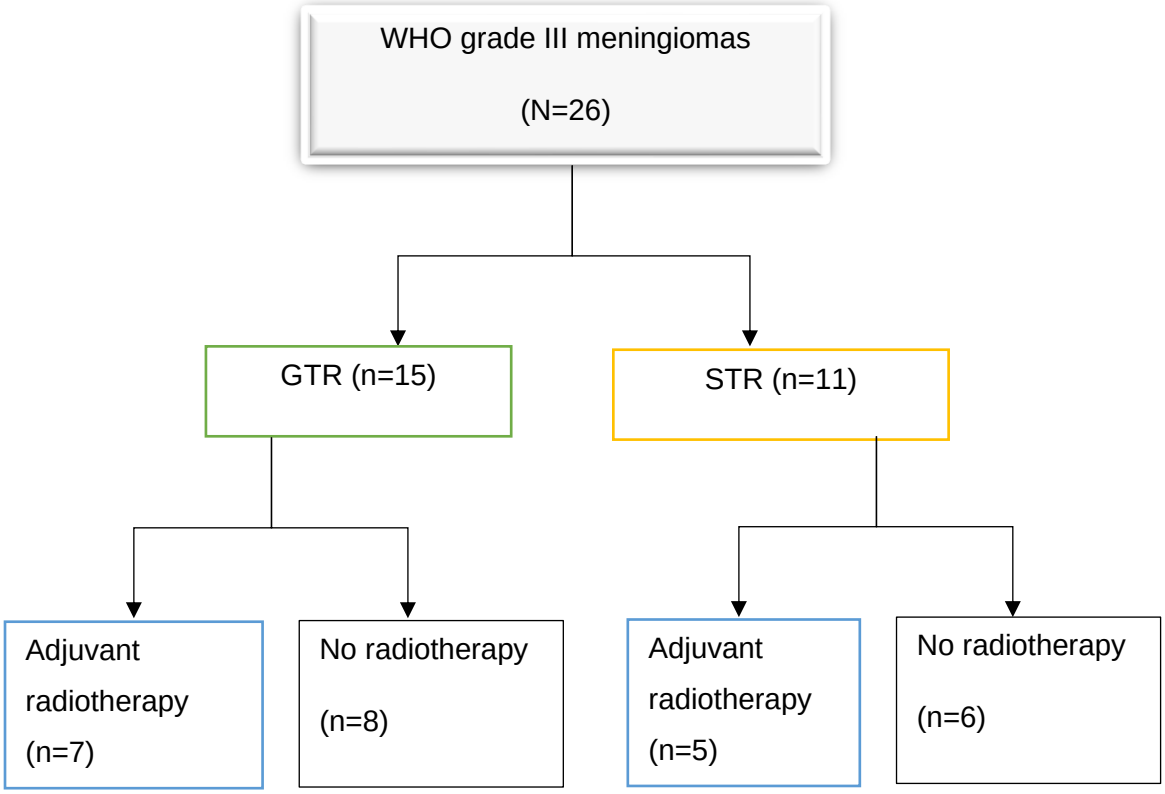


Figure 2. Diagram of the treatments patients with WHO grade III meningiomas underwent at CHUC. GTR, gross total resection; STR, subtotal resection.

At data collection, 18 patients (69.2% of the total) were deceased. The median follow-up of the 8 patients (30.8%) who were alive at censoring date was 4.48 years.

All patients were Portuguese nationals (white). According to the medical records, no patient had a known history of neurofibromatosis or other genetic syndromes.

Tables 1, 2 and 3 summarize the clinical, radiological and histopathological data of WHO grade III meningioma patients.

Table 1. Patient characteristics

PATIENT CHARACTERISTICS	
Male/female ratio	1.00
Age at grade III diagnosis	Median: 65.5 yrs Mean: 64.77 yrs Range: 28 - 83 yrs

Tumor location	• Convexity: 10 (38.5%)
	  ○ Frontal convexity: 6 (23.1%)
	  ○ Parietal convexity: 3 (11.5%)
	  ○ Occipital convexity: 1 (3.8%)
	• Parasagittal/falx: 9 (34.6%)
	• Clinoidal: 2 (7.7%)
	• Sphenoid wing/ cavernous sinus: 2 (7.7%)
	• Tentorium: 2 (7.7%)
	• Olfactory groove: 1 (3.8%)

Symptoms before grade III diagnosis	• Headache: 14 (53.8%) • Dysphasia/aphasia: 8 (30.8%) • Visual disturbances: 7 (26.9%) • Contralateral (relative to tumor site) hemiparesis: 7 (26.9%) • Cognitive problems: 4 (15.4%) • Seizure: 2 (7.7%)
Simpson grade	• Simpson I: 9 (34.6%) • Simpson II: 6 (23.1%) • Simpson IV: 11 (42.3%)
Previous non-grade III diagnosis in meningiomas who underwent malignant transformation	16 (61.5%)* Excluding 1 unknown previous histology, the former meningioma grades, subtypes and respective percentage relative to the known previous histologic subtypes were: • Atypical (WHO grade II): 9 (60%) • Transitional/mixed (WHO grade II): 2 (13%) • Meningothelial (WHO grade I): 2 (13%) • Chordoid (WHO grade II): 1 (7%) • Fibrous/ fibroblastic (WHO grade I): 1 (7%)
Time to malignant transformation† from WHO grade I or II	• Median= 70 months • Mean= 85 months • Range=7 months – 218 months

Adjuvant radiotherapy (after grade III surgery)	12 (46.2%) • External beam radiation therapy (EBRT): 11 • Intensity-modulated radiation therapy (IMRT): 1 • Dynamic conformal arc single-session stereotactic radiosurgery (SRS): 1 (this patient received both this treatment and external radiotherapy at different times after grade III diagnosis)

Adjuvant medical treatment for meningioma (chemotherapy and/or hormone-directed-therapy; excludes corticosteroids)	• No: 22 (84.6%)
	• Yes: 4 (15.4%)
	  ○ Temozolomide: 2 (7.7%)
	  ○ Tamoxifen: 1 (3.8%)
	  ○ Tamoxifen + hydroxyurea: 1 (3.8%)

Grade III meningiomas that had recurred or led to death at censoring date	23 (88.5%)
Karnofsky Performance Status (KPS)	• 100%: 1 (3.8%) • 90%: 8 (30.8%) • 80%: 3 (11.5%) • 60%: 4 (15.4%) • 50%: 3 (11.5%) • Unknown: 7 (26.9%)
Number of surgeries for grade III meningioma	• Mean: 1.77 • Median: 1 • Range: 1-7
Total number of surgeries (non-grade III + grade III meningioma)‡	• Mean: 2.69 • Median: 2 • Range: 1-9
Perioperative complications (first WHO grade III meningioma surgery)	• None: 15 (57.7%) • CSF leak: 5 (19.2%) • Infection (systemic/respiratory/urinary): 4 (15.4%) • Excessive bleeding during surgery: 1 (3.8%) • Deep venous thrombosis: 1 (3.8%)
Personal history of non-central nervous system malignancies§	• None: 10 (38.5%) • Unknown: 9 (34.6%) • Uterine fibroids: 4 (15.4%; 30.8% in the female population) • Benign fibrous histiocytoma: 1 (3.8%) • Bladder cancer: 1

	• Gastrointestinal stromal tumor: 1 • Lipoma: 1 • Tumor of the hepato-pancreato-biliary system: 1
Depressive symptoms due to meningioma diagnosis	6 (23.1%)

* One of the papillary meningiomas was secondary and underwent transformation from an atypical meningioma. The rhabdoid meningioma was diagnosed in a patient with history of a meningothelial meningioma (see illustrative case).

† The term “malignant” here exceptionally refers to all WHO grade III histologic subtypes (anaplastic, papillary and rhabdoid); we also use “transformation” instead of progression to avoid confusion with meningiomas that recurred.

‡ Including biopsies but excluding shunt revisions and CSF leak repairs.

§ Some patients had a history of more than one non-central nervous system malignancy.

Table 2. Radiological findings in WHO grade III patients

RADIOLOGICAL FINDINGS	
Tumor size (greatest diameter in centimeters)	4.00 cm (median; clearly reported in 16 cases)
Venous sinus invasion	Present: 13 (50%). Relative percentages: • Superior sagittal sinus: 9 (69.2%) • Cavernous sinus: 2 (25.4%) • Straight sinus (and vein of Galen): 1 (7.7%)
Bone invasion	14 (53.8%)
Peritumoral edema	15 (57.7%)
Extracranial extension	10 (38.5%)

Table 3. Histopathological findings in WHO grade III patients

HISTOPATHOLOGICAL FINDINGS	
Number of mitoses per 10 high power fields	○ >20: 23 (88.5%) ○ Exact number not specified: 15 (57.7%) ○ >20 but <30: 5 (mean of 23.8) (19.2%) ○ >30 but <40: 1 (3.8%) ○ >40 but <60: 2 (7.7%) ○ 15-20: 2 (7.7%, both papillary) ○ Not specified: (3.8%, rhabdoid)
Ki-67 index	Of the pathological reports (13) with specific Ki-67 index reported (mutually exclusive groups): ○ >8%: 2 (15.4%) ○ >15%: 7 (53.8%) ○ >20%: 3 (23.1%) ○ >40%: 1 (7.7%)
Necrosis	19 (73.1%)
Brain invasion	19 (73.1%)
Progesterone receptors	Of the 5 cases screened for progesterone receptors: ○ Positive: 2 (40%) ○ Negative. 3 (60%)

Female/male ratio was 1.0. Median age at grade III diagnosis was 65.50 years (with a standard deviation of 12.76 years). A significant proportion (61.5%) of the patients in our case series had a previous history of a WHO Grade I or II meningioma. From the available data, we observed that the median and average time from the first non-grade III diagnosis to the diagnosis of a grade III meningioma (i.e., “time to transformation”) were 70 months and 85 months, respectively.

Almost half (46.2%) of patients received adjuvant radiotherapy after grade III meningioma surgery, but only 4 (15.4%) received adjuvant chemotherapy and/or hormone-directed therapy (for details, see Table 1). While we were able to compare survival between groups treated with adjuvant radiotherapy and those who were not, we were not able to do the same for chemotherapy considering it was used so infrequently.

Of note, patients in our series underwent an average of 1.77 surgeries for a WHO grade III meningioma (including primary surgery and operations for recurrences), and an average total

of 2.69 procedures for meningioma (of any WHO grade) resections (including primary surgery and surgeries due to tumor recurrence).

At the time of grade III meningioma diagnosis, we observed venous sinus invasion, bone invasion and peritumoral edema in 50%, 53.8% and 57.7% of patients, respectively, demonstrating the aggressive behavior of these meningiomas.

Furthermore, almost a quarter (23.1%) of patients showed depressive symptoms due to their meningioma diagnosis.

Taking into account all patients, median overall survival was 2.45 years (95% CI: 1.05; 3.85) and median progression-free survival was 1.22 years (95% CI: 0.46; 1.98) (Table 4). No death occurred within 1 month after WHO grade III diagnosis/surgery. Figure 3 shows the Kaplan-Meier overall and progression-free survival curves for all our patients.

Table 4. Survival rates for all WHO grade III meningiomas in our series

	1-yr	2-yr	3-yr	5-yr	10-yr	Median	Mean
Overall survival	73%	57%	45%	35%	23%	2.45 (95% CI: 1.05; 3.85) yrs	3.92 (95% CI: 1.90; 5.94)
Progression-free survival	65%	42%	31%	13%	0%	1.22 (95% CI: 0.46; 1.98) yrs	1.80 (95% CI: 1.18; 2.41) yrs

CI, Confidence Interval; yr/s, year/s.

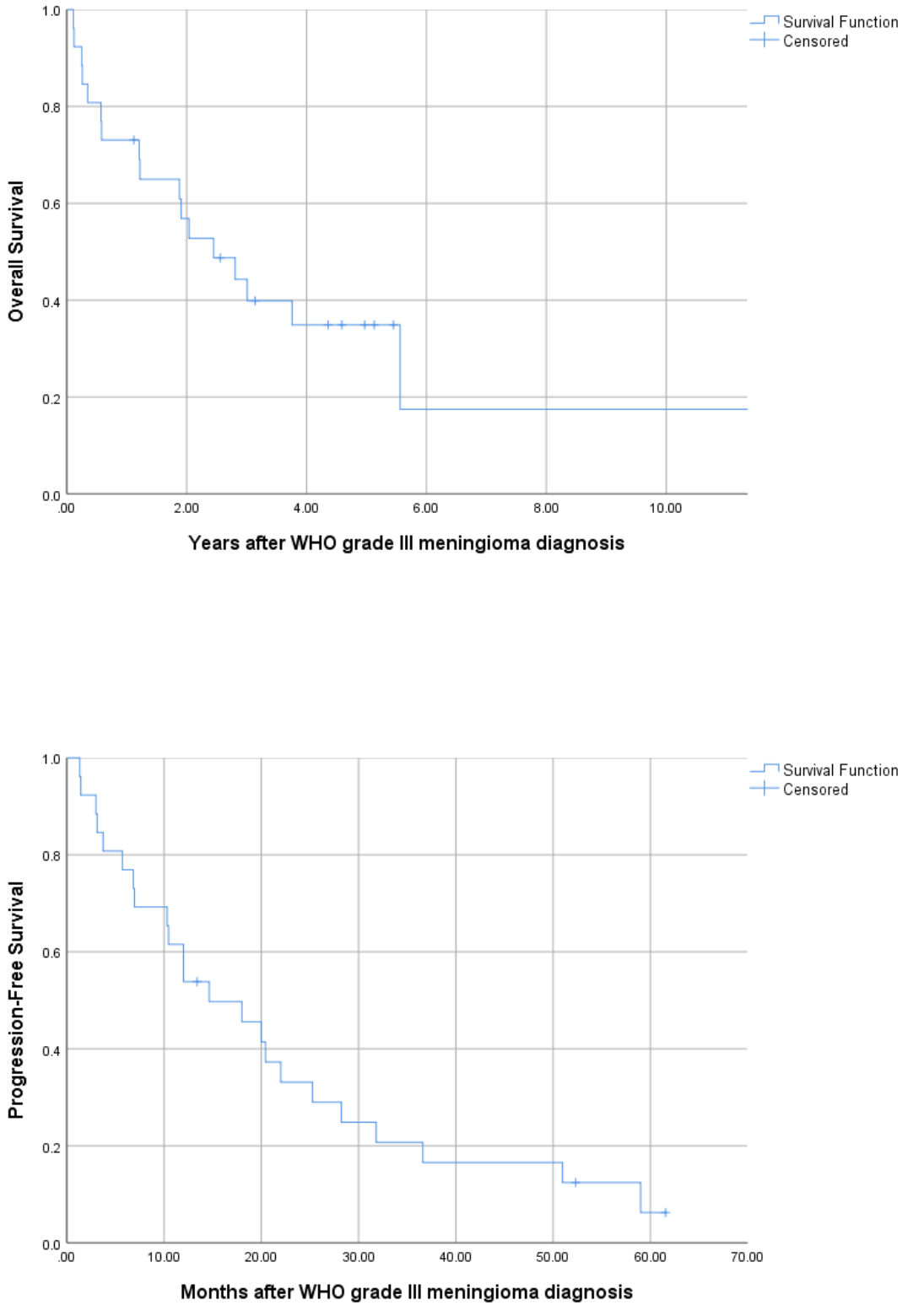


Figure 3. Kaplan-Meier overall survival (OS) and progression-free survival (PFS) curves for all WHO grade III meningioma patients in the present case series.

The log-rank test comparing survival between patients with anaplastic meningiomas and patients with papillary/rhabdoid meningiomas was non-significant (p=0.800), although this may be due to the very small number of papillary and rhabdoid meningiomas in our series. Tables 5 and 6 provide separate survival information per histologic subtype.

Table 5. Survival rates for anaplastic meningiomas in our series

	1-yr	2-yr	3-yr	5-yr	Median	Mean
Overall survival	70%	56%	46%	35%	2.81 (95% CI: 1.26; 4.37) yrs	4.91 (95% CI: 2.78; 7.05) yrs
Progression-free survival	57%	34%	24%	8%	1.50 (95% CI: 0.32; 2.68) yrs	1.85 (95% CI: 1.16; 2.54) yrs

CI, Confidence Interval; yr/s, year/s.

Note: Because in the case of anaplastic meningiomas all but one case were censored after 5 years of follow-up, the 10-yr OS rate showed up as equal to 5-yr OS rate and was thus eliminated from this table.

Table 6. Overall and progression-free survival for papillary and rhabdoid meningiomas in our series

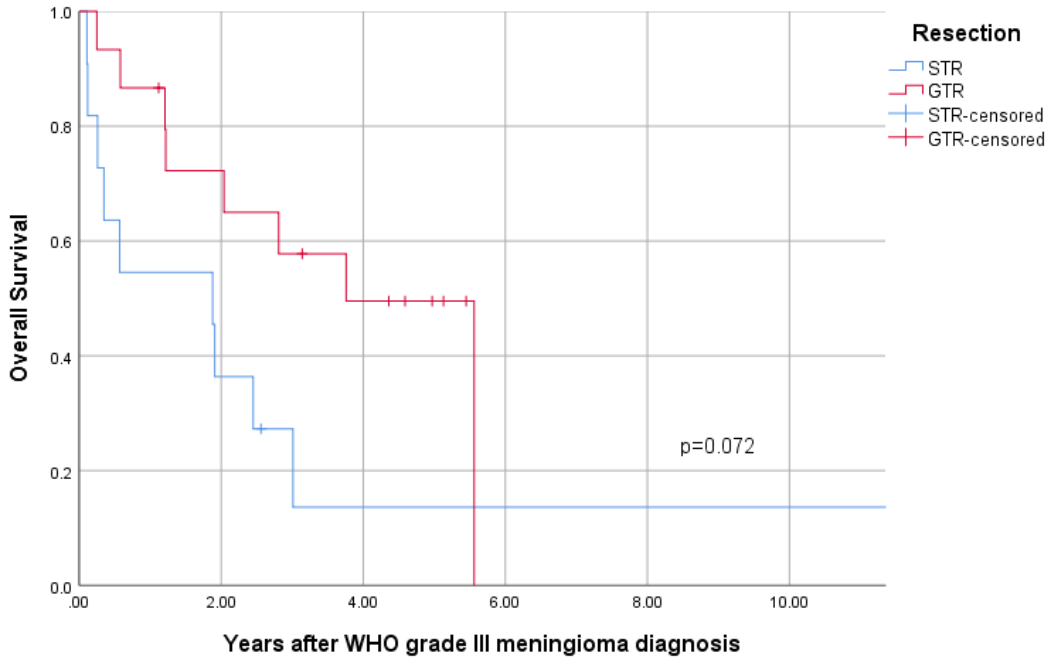
	Papillary (case 1)	Papillary (case 2)	Rhabdoid
Overall survival	1.22 yrs	2.45 yrs	5.56 yrs
Progression-free survival	Died before recurrence occurred (PFS=OS)	1.25 yrs	2.08 yrs

Yr/s, year/s.

Regarding extent of resection, there was a trend toward improved survival with gross total resection when compared to subtotal resection (p=0.072), but the p-value, while approaching significance, did not reach it (Figure 4). There was also no statistically significant difference in overall and progression-free survival between meningiomas which underwent Simpson grade I resections and those that corresponded to non-Simpson grade I resections (Figure 5). Table 7 also provides an overview of the Simpson grades of resection relative to the location of the meningiomas. We note that the location of the two tentorial/ posterior fossa meningiomas (one rhabdoid and one papillary) made complete resections more difficult, especially with the uncontrolled growth and the invasion of nearby structures by these tumors.

Table 7. Tumor location and Simpson grade

	Simpson grade I	Simpson grade II	Simpson grade IV
Convexity	4 frontal 1 parietal 1 occipital	1 parietal	2 frontal 1 parietal
Parasagittal/falx	1	4	4
Clinoid		1	1
Sphenoid wing/ cavernous sinus			2
Tentorium	1 (surgery repeated after subtotal resection 2 weeks before)		1
Olfactory groove	1		



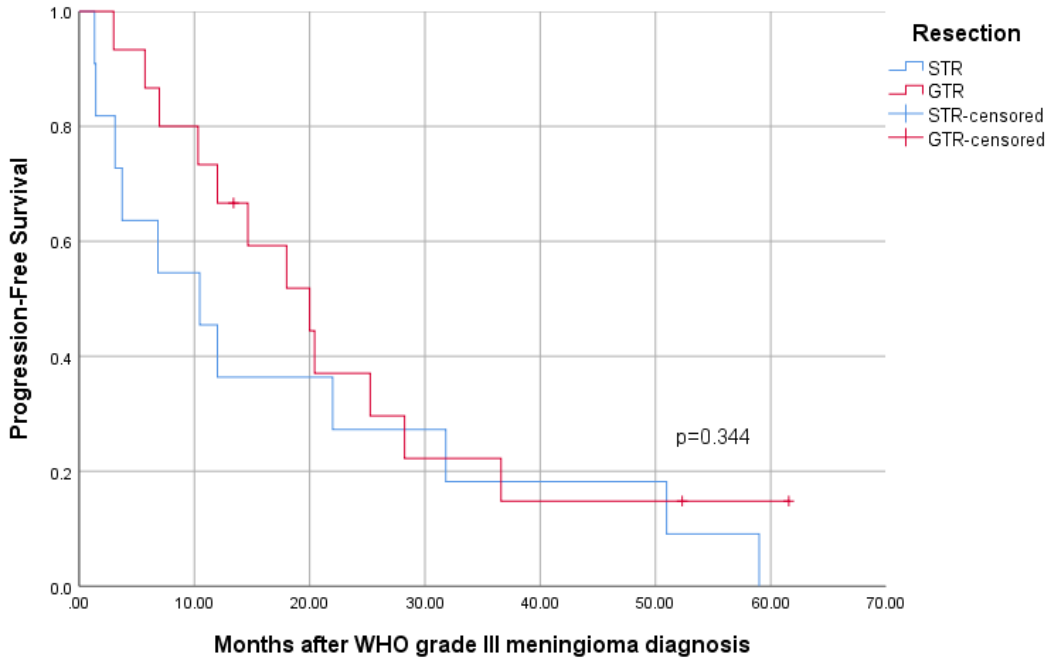
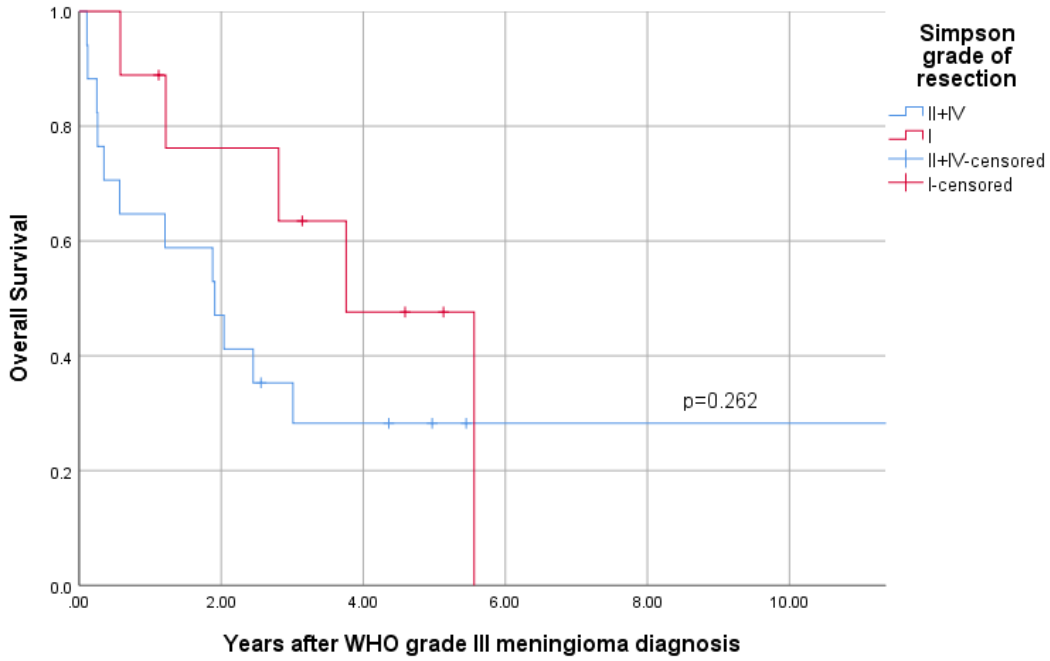


Figure 4. Kaplan-Meier OS and PFS curves comparing patients with gross total resection (Simpson grades I+II) and patients with subtotal resection (Simpson grade IV).



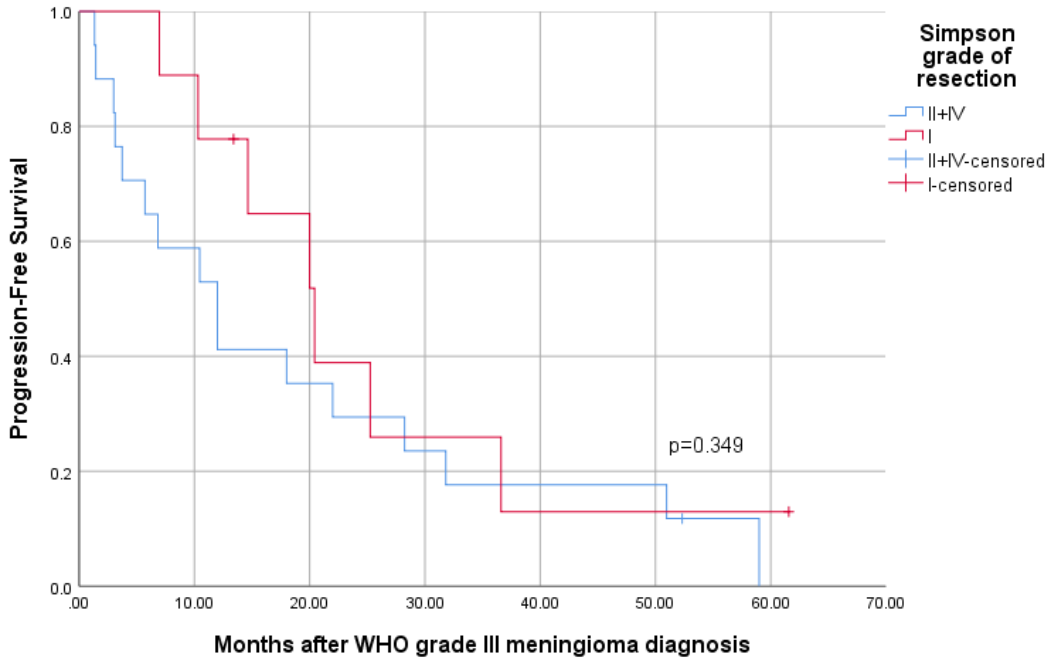
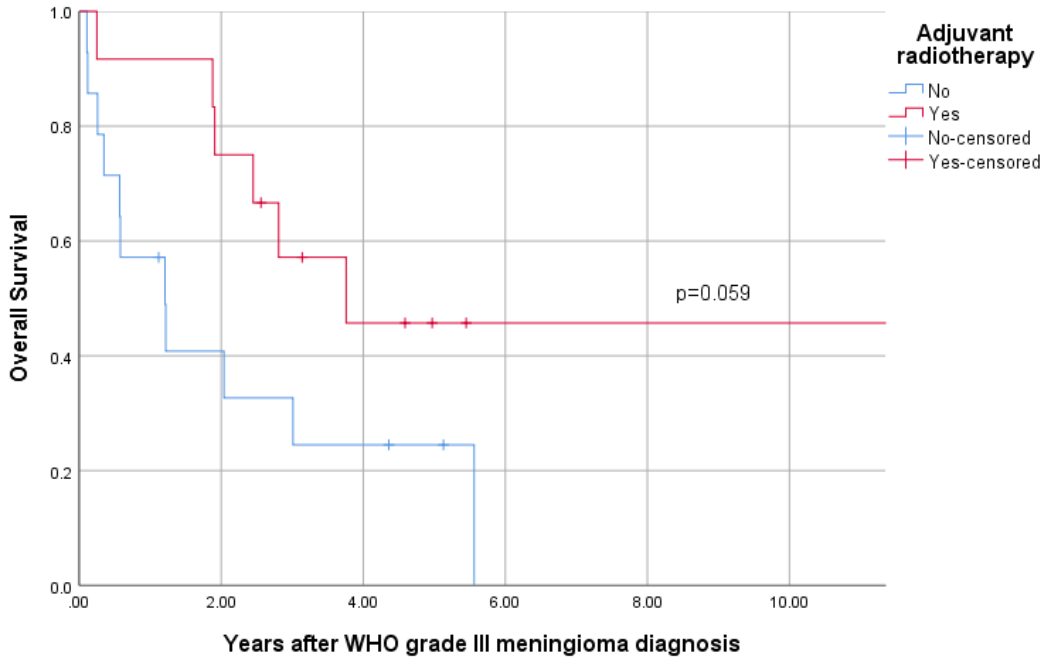


Figure 5. Kaplan-Meier OS and PFS curves comparing patients with Simpson grade I resections and patients with Simpson grades II+IV resections.

The use of adjuvant radiotherapy was very close to showing a statistically significant improved survival for grade III meningiomas in general using the univariate log-rank test (p=0.059) (Figure 6). However, the use of adjuvant radiotherapy did correlate significantly with improved survival in the case of subtotally resected meningiomas (Figure 7, bottom). As the number of patients with STR meningiomas was small (n=11), we used a separate multivariate Cox regression analysis for the STR subgroup with the most relevant factors as covariates (adjuvant radiotherapy vs. surgery alone; age≥ 70 vs. age<70 years; secondary vs. primary meningioma; female vs. male), which still showed that adjuvant radiotherapy improved survival in STR meningiomas (p=0.011).

Moreover, log-rank tests also revealed that adjuvant radiotherapy did not significantly improve progression-free survival (PFS) in grade III meningiomas in general when compared to surgery alone (p=0.873) (Figure 6, bottom). Although not represented graphically, adjuvant radiotherapy also failed to improve PFS in the case of GTR meningiomas (p=0.482), but there was a trend toward improved PFS with adjuvant radiotherapy in STR meningiomas (p=0.068) using univariate analysis.



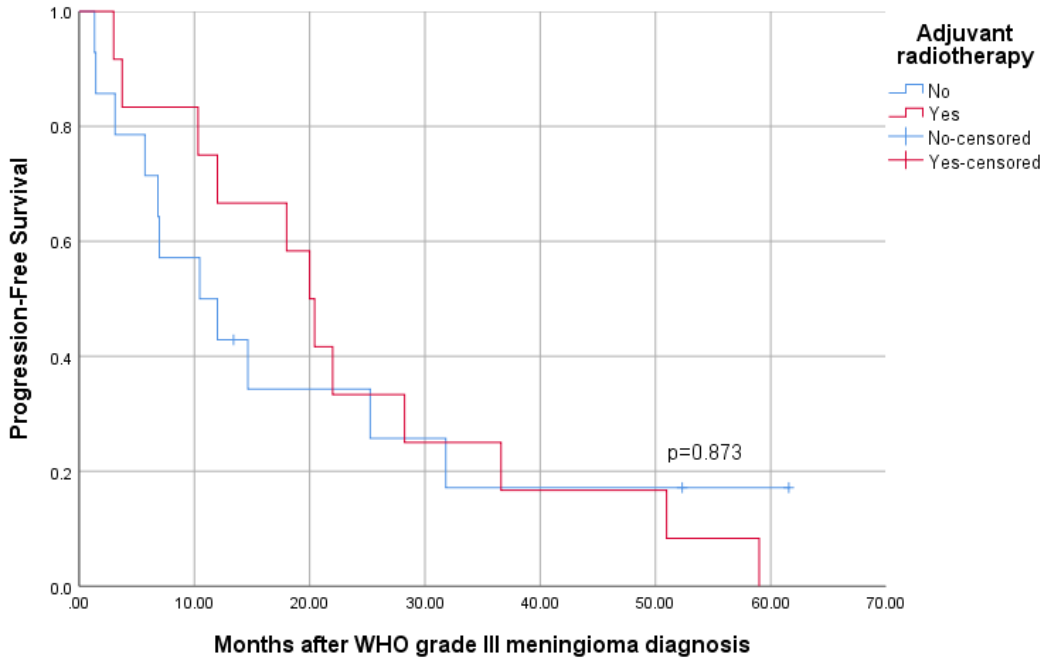


Figure 6. Kaplan-Meier OS and PFS curves comparing all patients who received adjuvant radiotherapy after surgery and patients who underwent surgery alone.

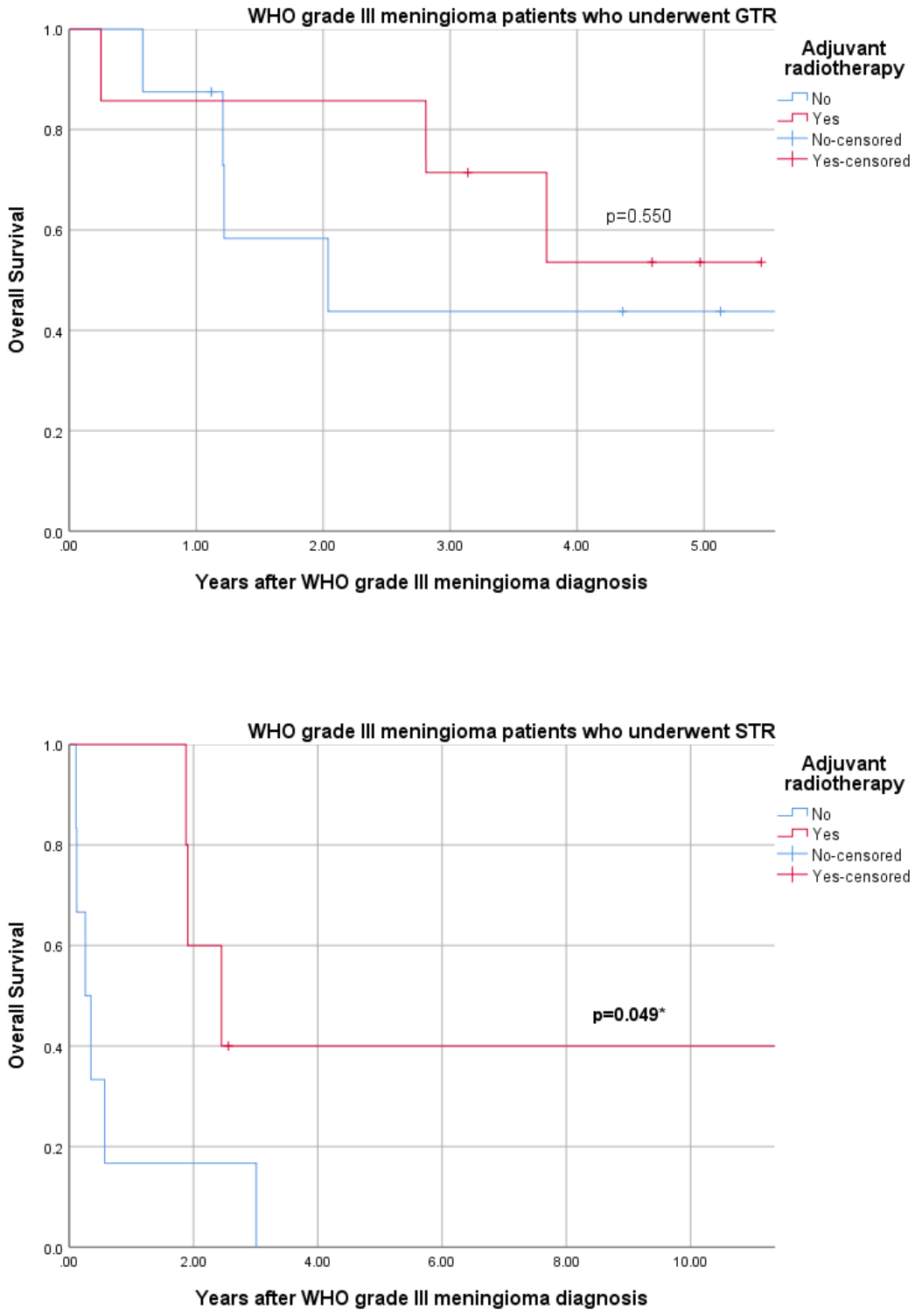


Figure 7. Kaplan-Meier OS curves comparing adjuvant radiotherapy after surgery vs. surgery alone in GTR and STR patients.

Tables 8 and 9 show the results for the univariate log-rank (Mantel-Cox) tests and the multivariate Cox regression analysis, respectively, for all WHO grade III meningiomas in the present case series. Although adjuvant radiotherapy did show improved survival on multivariate analysis for the whole group of grade III meningiomas, the fact that adjuvant radiotherapy only conferred a significant survival benefit in the case of subtotally resected meningiomas and not for gross totally resected ones warrants caution in assuming that adjuvant radiotherapy is indeed beneficial for all grade III meningiomas in general.

Table 8. Log-rank (Mantel-Cox) tests for overall survival (univariate analysis)

Variable	P-value
GTR vs. STR	**0.072***
Simpson I vs. II+IV	0.262
Adjuvant radiotherapy vs. surgery alone	**0.059***
Age≥ 65 vs. age<65 years	0.779
Age≥ 70 vs. age<70 years	0.321
Secondary vs. primary grade III meningioma	0.558
Female vs. male	0.871
Convexity vs. non-convexity	0.796
Brain invasion (yes vs. no)	0.344
Venous sinus invasion (yes vs. no)	0.616
Bone invasion (yes vs. no)	0.419

*p<0.10

Table 9. Multivariate Cox regression for overall survival of all patients in our series*

	B	SE	Wald	df	Sig.	HR†	95% CI for HR	
							Lower	Upper
GTR vs. STR	-1.696	1.017	2.777	1	.096	.184	.025	1.348
Adjuvant radiotherapy vs. surgery alone	-1.639	.739	4.923	1	**.027**	.194	.046	.826

*Covariables considered: GTR vs. STR; adjuvant radiotherapy vs. surgery alone; age≥ 70 vs. age<70 years; secondary vs. primary meningioma; female vs. male; convexity vs. non-convexity; brain invasion, venous sinus invasion; bone invasion.

† HR, hazard ratio.

Progression-free survival rates by themselves do not provide a true picture of the clinical course of patients with grade III meningiomas, as these have both a complex previous history as well as progression after grade III diagnosis. Thus, we chose to create a table in a similar way to that presented by Al-Mefty et al.[13] to better illustrate the clinical course of patients with ≥2 recurrences previous to grade III and/or ≥2 recurrences after initial grade III surgery (Table 10). The intervals listed in this table only refer to intervals between surgeries (histopathological diagnoses), and in our progression free survival analysis we used the time to symptomatic relapse/radiological recurrence whenever available to calculate time to progression/recurrence. When these data were not available, we used the time of second surgery to calculate time to progression.

Although we only considered grade III diagnoses since 2000, some of the patients included in Table 10 received a WHO grade I or II meningioma diagnosis before 2000. We confirmed, however, that none of the histopathological diagnoses predated the 1993 WHO Classification of Tumors of the Central Nervous System.[14]

Table 10. Surgeries and respective pathological diagnoses for meningiomas with more than one recurrence

Gender, Age (first meningioma diagnosis – any grade)	1st diagnosis	1st interval	2nd diagnosis	2nd interval	3rd diagnosis	3rd interval	4th diagnosis	4th interval	5th diagnosis	Outcome at end of our study
Female, 42 yrs*	Atypical (GII), Simpson I	35 mos	Atypical (GII), Simpson grade IV	40 mos	Anaplastic (GIII), Simpson grade IV	59 mos (RT)	Atypical with areas of chordoid meningioma (GII)	21 mos	Atypical (GII); Simpson grade IV (multiple (3) meningiomas)	Dead 11.36 yrs after GIII diagnosis (17.54 yrs after initial meningioma surgery)
Male, 63 yrs	Chordoid (GII), Unknown grade of resection	99 mos	Chordoid (GII), Unknown grade of resection	119 mos	Anaplastic (GIII); Simpson grade I removal of multiple meningiomas (3)	--	--	--	--	*Alive* and mostly asymptomatic at 5.12 yrs after initial GIII diagnosis (23.29 yrs after initial meningioma surgery)†

Female, 66 yrs	Transitional (GI) with "atypical features", Simpson grade IV	4 mos	Transitional (GI) with "atypical features", Simpson grade IV	124 mos (RT)	Anaplastic (GIII), Simpson grade I	20 mos (IMRT)	Tumor recurrence (Brain Tumor Board decided surgery was not indicated)	8 mos	--	Dead 3.76 years after GIII diagnosis (14.42 yrs after initial meningioma surgery)
Male, 63 yrs	Atypical (GII), Simpson grade II	19 mos	Anaplastic (GIII), Simpson grade II	18 mos (RT)	Anaplastic (GIII), Simpson grade II (deduced from operative note)	12 mos	Anaplastic (GIII), Simpson grade II (deduced from operative note)	--	--	*Alive* at 2.96 yrs after GIII diagnosis (4.51 yrs after initial meningioma diagnosis)
Female, 49 years	Atypical (GII), Simpson grade II (deduced from operative note and post-op CT)	40 mos	Atypical (GII), Simpson grade II	88 mos (RT)	Right frontal meningioma: Anaplastic (grade III), Falx: Atypical (grade II), Simpson grade IV	3 mos	--	--	--	Dead 0.26 yrs after GIII diagnosis (10.99 yrs after initial meningioma surgery)

Male, 41 yrs	Transitional (GI), Simpson grade IV	116 mos (stereotactic RT at 42 mos)	Transitional (GI), Simpson grade V (biopsy)	6 mos	Anaplastic (GIII), Simpson grade II	12 mos	Tumor regrowth on MRI	13 mos	--	Dead 2.04 yrs after GIII diagnosis (12.24 yrs after initial meningioma surgery)
Male, 50 yrs	Papillary (GIII), Simpson grade IV	15 mos (SRS)	"Anaplastic" (GIII) ‡ from outside hospital (Germany), Simpson grade IV	9 mos (RT)	Papillary (GIII), Simpson grade II (deduced from operative note and post-op CT)	3 mos	--	--	--	Dead 2,46 yrs after grade III (=initial meningioma) diagnosis
Male, 23 yrs	*See illustrative case (Figure 8)*									

Abbreviations: GI, WHO grade I meningioma; GII, WHO grade II meningioma; GIII, WHO grade III meningioma; Mos, months; Yrs, years; Wks, weeks.

IMRT – patient received Intensity-Modulated Radiation Therapy in this interval 11 months after last surgery.

RT – patient underwent radiotherapy in this interval soon (generally weeks to 3 months) after last surgery.

SRS – patient underwent stereotactic radiosurgery in this interval 2.5 months after last surgery.

Notes:

*This was the only patient in our series whose grade III meningioma recurred as a grade II (atypical) meningioma.

† Although control MRI has shown a small growth of residual tumor, we interpreted this as a non-recurrence as the patient remained almost fully asymptomatic and did not need treatment.

‡ Possibly, the tumor was named “anaplastic” by this outside hospital because it was classified as WHO grade III, and not necessarily because it had anaplastic histology. Of all the surgeries in this article, this was the only one which was performed outside the Portuguese National Health Service.

Illustrative case: Rhabdoid meningioma

In the mid-1990s, a 23-year-old right-handed white male presented to the emergency department at our hospital after referral from an ophthalmologist who had detected bilateral papilledema on fundoscopy the day before. This young patient admitted to having visual acuity difficulties that were more pronounced on the left approximately one year before his referral, but to which had not paid much attention. However, ever since 3 months before, he had started having occipital headaches predominantly in the morning, which were aggravated with movement. The appearance of these headaches was accompanied by a deterioration in his visual acuity. This patient had unremarkable past medical history except for chickenpox (varicella zoster virus infection) at the age of 18. He denied any history of head trauma. Regarding possible environmental factors that have been investigated in meningiomas[15, 16], he denied any allergies and, according to him, he did not smoke. We could not find any childhood history of malignancies nor of radiation therapy.

On physical exam, the patient had bilateral loss of vision acuity, bilateral papilledema worst on the left eye with retinal hemorrhages, unsteady tandem gait and a slightly positive Romberg's sign. CT head revealed a posterior fossa mass extending into the fourth ventricle as well as hydrocephalus. The patient was operated days later with total removal of the lesion and a shunt was placed. A diagnosis of meningothelial (benign) meningioma, according to the 1993 WHO Classification of Tumors of the Central Nervous System[14], was made. Two days after surgery, a control CT revealed a post-operative hematoma compressing the fourth ventricle. Six days after surgery, upon removal of bandages, a CSF leak was noted, which only resolved two weeks later.

Almost exactly four years after the initial surgery, the patient was re-operated due to worsening visual acuity and a CT showing tumor recurrence at the tentorium. Gait abnormalities, speech difficulties and right-beating nystagmus had begun to be noticeable since approximately one year and 3 months after the initial surgery. In his second surgery, a Simpson grade II removal of the tumor was achieved and pathology revealed again a meningothelial meningioma, with no detectable mitoses nor necrosis. Postoperatively, the patient maintained vision difficulties and his CSF leak recurred.

Ten months after the second surgery, the patient had to be re-operated due to continuous worsening of his visual acuity; this third time, only a subtotal resection was achieved as patient positioning at the time made it difficult to access the tumor. Thus, a week later, the patient had his fourth surgery in order to achieve complete resection (hence being interpreted as a gross total resection in our survival analysis). These last two surgeries, roughly five years after initial benign meningioma diagnosis, led to the discovery of a rhabdoid meningioma. Although some

mitotic figures where noted upon histopathological examination, no necrosis was observed. Besides his persistent marked vision problems, the patient felt extremely depressed, so a referral to a psychiatrist was also made.

Over the following years, the patient underwent repeated procedures for his tumor: his fifth and sixth surgeries two years after initial rhabdoid meningioma diagnosis (one for tumor removal and the second for CSF leak repair), then again a seventh and eighth surgical interventions roughly 2 years after. Nine years and 7 months into his disease (almost 5 years after a grade III diagnosis) the patient experienced a “massive” regrowth of his tumor, and only two subtotal resections (within a 4-month interval) were possible at the time due to frank invasion of critical structures, namely the brainstem. Around 4 months after the last subtotal resection, and 5 years and 7 months after his first grade III diagnosis, this young patient died due to periods of apnea and prolonged hypotension unresponsive to medical therapy.

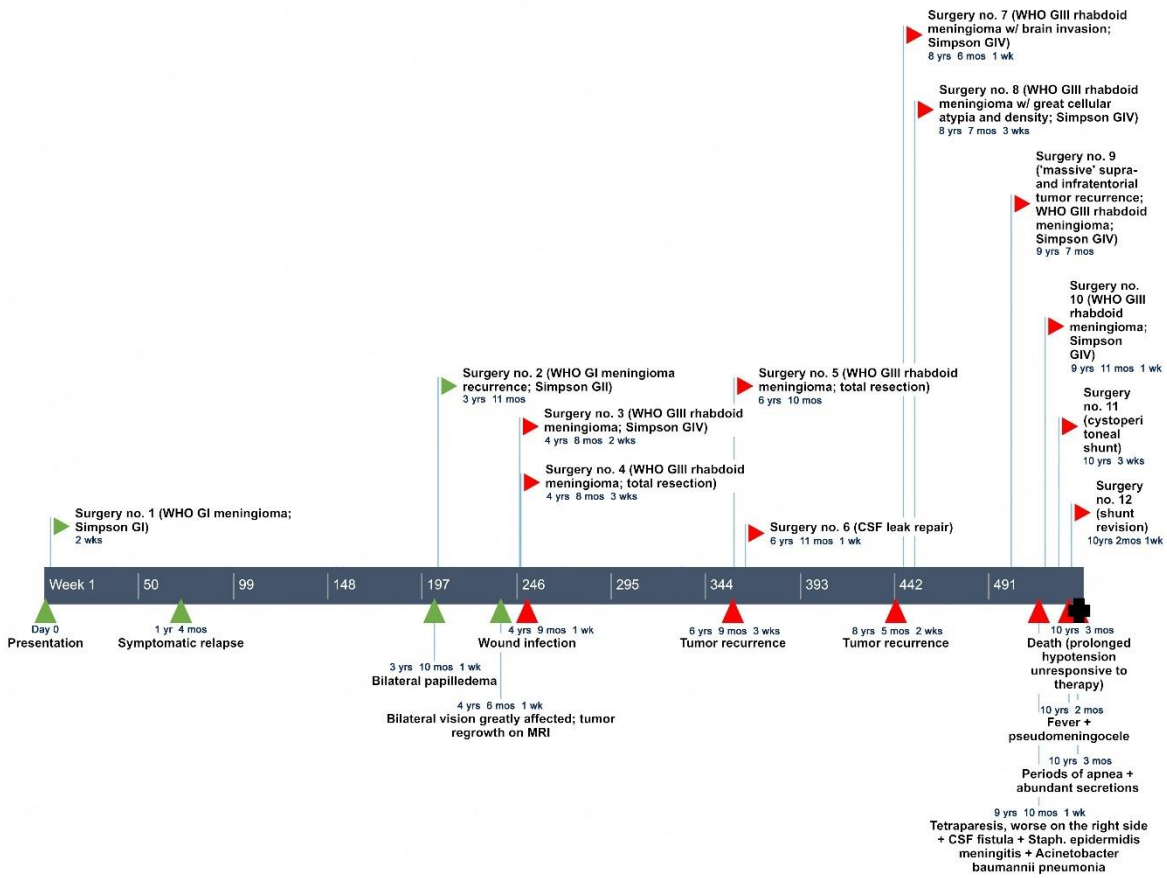


Figure 8. Timeline of a patient who was ultimately diagnosed with a rhabdoid meningioma. Dates refer to time elapsed since his first meningioma surgery (when he was 23), which led to the diagnosis of a WHO grade I meningioma. He died roughly 5 years and 7 months after his initial grade III meningioma diagnosis.

Discussion

Extent of resection

Table 11 provides a comparison between our study and the WHO grade III meningioma studies published in recent years. Although some studies have shown improved survival with better extents of surgical resection of these tumors, others (like ours) have failed to provide a statistically significant overall survival benefit with gross total resections.

We must also stress that the terms gross total and subtotal resections do not bear uniform meanings in the literature. For instance, while the second edition of *Al-Mefty's Meningiomas* uses GTR (gross total) for Simpson grade I–III resections and STR (subtotal) for Simpson grade IV (sometimes IV+V) resections[17], an article co-authored by the same greatly influential neurosurgeon defined, in 2000, gross total resection as Simpson grades I+II, near-total resection as Simpson grade III and subtotal removal as Simpson grade IV; leaving grade V to correspond to biopsy alone.[18]

Despite the trend toward better survival with gross total resection of these meningiomas observed in our study, subtotal resections were many times made unavoidable by the invasion of critical structures, such as brain tissue and venous structures. Thus, subtotal resections may be an additional consequence of invasion of critical brain structures and not an independent cause of diminished survival. Still, we highly agree with the notion that the neurosurgeon should put forth his or her best efforts in attempting a maximal surgical resection of a WHO grade III meningioma.[19]

Radiotherapy and survival benefit

In our study, adjuvant radiotherapy after surgery proved to be an independent prognostic factor for grade III meningioma patients in general. However, when looking at the effect of adjuvant radiotherapy in each resection subgroup (GTR and STR), we observed that adjuvant radiotherapy, when compared to surgery alone, only significantly improved survival in the case of subtotally resected meningiomas. Other studies have found improved survival with adjuvant radiotherapy for all WHO grade III meningiomas, irrespective of grade of resection.[20-22] However, we must stress that retrospective studies in this sense are very much prone to bias, as patients who underwent radiotherapy had to live long enough in order to be considered for and subjected to this treatment, whereas there might have been patients who died before getting the opportunity to be receive radiotherapy. We had at least two cases of patients who

were scheduled for radiotherapy, but one died (due to rapid tumor progression) before receiving this treatment and the other was ultimately deemed too debilitated to receive any further treatment (hence her prognosis was already poor). Unfortunately, due to the relative low number of cases, we were not able to study survival differences between patients treated with different radiation treatment modalities nor the impact on survival that the timing of radiotherapy after grade III meningioma surgery might have.

Nevertheless, the fact that radiotherapy offered a significant survival benefit for STR meningiomas, and not for GTR meningiomas, poses the question of whether radiotherapy should only be considered for patients whose meningiomas could only be partially resected. Indeed, radiotherapy is not without its side effects and even glioblastomas induced by radiosurgery for meningiomas have been reported.[23, 24]

Table 11. Summary of single-center and multicenter studies focusing on WHO grade III meningiomas published between 2010-2020

Authors (country/ region, year)	Years of inclusion	Histologic subtypes				Age at surgery or diagnosis	Male/ female ratio	OS	PFS	Adjuvant RT improved survival?	Extent of resection correlated with survival?	Definitions of GTR/ NRR/ RR/ STR/ TR (in terms of Simpson grade)
		Anaplastic	Papillary	Rhabdoid	Subtype not *clearly* specified							
This study (Portugal, 2020)	2000-2018	23	2	1		65.5 yrs (median) 64.77 yrs (mean) 28 - 83 yrs (range)	1.00	2.45 yrs (median)	1.22 (median)	For STR tumors, but not for GTR ones (OS) No (PFS)	No (trend observed)	GTR=I+II STR=IV
Champeaux et al.[20] (France & United Kingdom, 2019)	1989-2017				178	62.7 yrs (median)	1.02 (from table of data)	2.9 yrs (median)		Yes (OS)	Yes	GTR=I+II+III Total resection=I+II STR=III+IV+V

Masalha et al.[25] (Germany, 2019)	2001-2016	29				61.2 yrs (mean)	0.93 (from table of data)	1-yr OS: 62.5% (surgery) and 71% (surgery+ RT)		No (OS) Yes (PFS)	Yes	GTR=I+II STR=III+ IV+V
Maier et al.[26] (Denmark, 2019)	2000-2014	16	4	4		61.6 yrs (mean)	0.85	3.88 yrs (median)	16.5 months		No	RR=I+II NRR=III+ IV
Peyre et al.[3] (France, 2018)	Not clearly stated	57				60 yrs (mean)	1.11	2.6 yrs (median)			Yes (only in de novo anaplastic meningiomas)	GTR and STR meaning not specified
Zhang et al.[21] (Beijing Tiantan Hospital, China, 2018)	2011-2015		12	11		Papillary: 42 yrs (mean) Rhabdoid: 38 yrs (mean)	Papillary: 0.71 Rhabdoid: 0.83	4.07 yrs (mean)		Yes (OS and PFS)	No	GTR=I+II STR=III+ IV
Zhang et al.[22] (Beijing Tiantan Hospital, China, 2018)	2008-2016	56				49 years (mean)	1.24	3.88 yrs (mean)	26.8 months (median)	Yes (OS and PFS)	Yes	GTR=I+II STR=III+ IV

Balasubramanian et al.[8] (USA, 2017)	2000-2015	17		1		63 yrs (median)	1.57	4.65 yrs (median) 3-yr OS: 69% 5-yr OS: 40%	14.5 mos (median)	No	No	GTR=I+II+III STR=IV
Moliterno et al.[27] (USA, 2015)	1999-2012	37				59 yrs (median)	0.76	2.7 yrs (median) 2-yr OS: 66.6% 5-yr OS: 27.9%			Yes	Not specified
Zhu et al. (Shanghai, China, 2015)[4]	2003-2008	63 (includes 2 spinal cases)				50.4 yrs (mean)	1.25	5.83 yrs (median) 3-yr OS: 68.3% 5-yr OS: 54.7%	52 mos (median) 3-yr PFS: 60.2% 5-yr PFS: 43.9%	Yes (PFS)	Yes (PFS) for 'non-recurrent' tumors; Did not influence PFS for recurrent tumors	I-II vs. III-IV
Wang et al.[28] (Shanghai, China, 2013)	1997-2011		30 (3 lost to follow-up)			34 yrs (median)	1.14		5-yr PFS: 26.9%	Yes (PFS)	Yes (in terms of PFS)	GTR=I+II STR=IV+V (Grade III not included).

Sughrue et al.[29] (USA, 2010)	Not specified				63	51 yrs (median)	0.66	2-yr OS: 82% 5-yr OS: 61% 10-yr OS: 40%		(All patients received adjuvant RT)	Inverse relationship: STR+EBRT had better survival than GTR+RT	Not clearly specified

EBRT, external-beam radiation therapy; GTR, Gross total resection; Mos, months; NRR, non-radical resection; OS, overall survival; PFS, progression-free survival; RR, Radical resection; RT, radiotherapy; STR, Subtotal resection; Yr/s, year/s.

Presence of metastases

Considering that these tumors were meningiomas, although of aggressive behavior, metastases were not actively sought for, as there are currently no evidence-based guidelines (at least in Europe[30]) for the staging of patients with WHO grade III meningiomas. Metastases can, however, be detected if a patient presents with signs of masses in other regions. Otherwise, *metastases from grade III meningiomas might go unnoticed*. We therefore cannot discard the possibility that metastases in our study were "underdiagnosed". The presence of metastases or microscopic tumor presence in other parts of the body might even prove a factor highly correlated with survival in grade III meningiomas, but our study and the current guidelines in practice did not allow us to conclude anything regarding this matter.

Primary (*de novo*) versus secondary WHO grade III meningiomas

In this study, primary grade III meningiomas failed to show statistically significant improved survival when compared to secondary tumors. In previous studies[3, 20], secondary meningiomas have been associated with a worse clinical outcome.

Location of grade III meningiomas

It was interesting to find that there was no grade III spinal meningioma in the present case series (spinal meningiomas are also included in the neuropathology database that was used for this study). In fact, some research has been published suggesting that grade III meningiomas are rare both in the skull base and in the spine.[31] Also, there is some evidence suggesting that non-skull base[32, 33] and cerebral convexity[34] locations in a meningioma confer it a higher risk of being a high-grade (grade II or III) meningioma.

Gender and WHO grade III meningiomas

In our study, we observed that half of the grade III meningioma patients were male. This is in contrast to the well-established fact that meningiomas in general are more common in women[35]. While this is in fact true for benign meningiomas, it seems that the female/male ratio of patients with grade III meningiomas is equal to or less than 1.[36] Although studies still report different female/male ratios (Table 11), our study is in line with what would generally be expected for WHO grade III meningiomas.

Temporal trend

The number of grade III meningiomas per year varied considerably between the 2000s and the 2010s at our institution, being clear from Figure 1 that the majority of cases happened between 2012 and 2018. There may be several explanations for this. Perhaps the likeliest explanation is the increase, over the years, in the use of CT imaging, which was not as widely used during the 2000s in Portugal as it is today. Also, in 2011, the Portuguese Government decided to fuse several hospitals of its National Health Service, leading to the merger of the Coimbra University Hospitals and the Coimbra Hospital Center. This process was only fully completed by the end of 2013. Moreover, some paper pathology reports, especially the ones from the 2000s, may not have been inserted electronically into our database. We do not think that revisions of the WHO Classification of Tumors of the Central Nervous System would have impacted grade III meningioma incidence, as this classification scheme has remained almost unchanged for grade III meningiomas since the year 2000.[37, 38] Thus, although we cannot fully exclude it, we do not believe that there was a true increase in the number of WHO grade III meningiomas in the last decade in central Portugal.

Histologic subtype and prognosis

If WHO grade III meningiomas in general are rare, papillary and rhabdoid meningiomas seem to be even more so. Therefore, any definite conclusions about their epidemiology and prognosis cannot be drawn due to the lack of substantial evidence in the literature. Although papillary and rhabdoid meningiomas seem to be associated with a better prognosis than anaplastic meningiomas just by looking at case series from the same institution[21, 22], it should also be noted that the mean age at diagnosis for the rhabdoid and papillary variants appears to be less than the average age at anaplastic meningioma diagnosis (our only rhabdoid meningioma patient was 28 years old and our two papillary meningioma patients were 50 and 75 years old when they were diagnosed with a grade III meningioma).

Intratumoral heterogeneity of meningiomas

We would like to highlight and discuss a few interesting findings in our case series that support the concept of intratumoral heterogeneity of meningiomas:

- One of the anaplastic meningiomas in our series had “papillary areas”, although their relative area was not sufficient to classify it as a papillary meningioma and was thus

considered an anaplastic meningioma in our analysis. This was the most recent case in our series and 1.12 years after receiving as sole therapy a Simpson grade I resection of his meningioma, this 71-year-old male has not had any recurrence of his tumor. Other researchers have already reported a case of a meningioma with mixed anaplastic and papillary subtypes.[39]

- A 62-year-old male (Figure 9) who first presented to our department with a large extracranial extension of his meningioma initially had a biopsy of this extracranial component which received the histopathological diagnosis of an atypical (WHO grade II) meningioma. Three weeks later, in an attempt to remove as much tumor as possible, the histopathological diagnosis of anaplastic meningioma was given. We chose to interpret this as a primary grade III meningioma case as the two surgeries were done within a relatively short space of time.

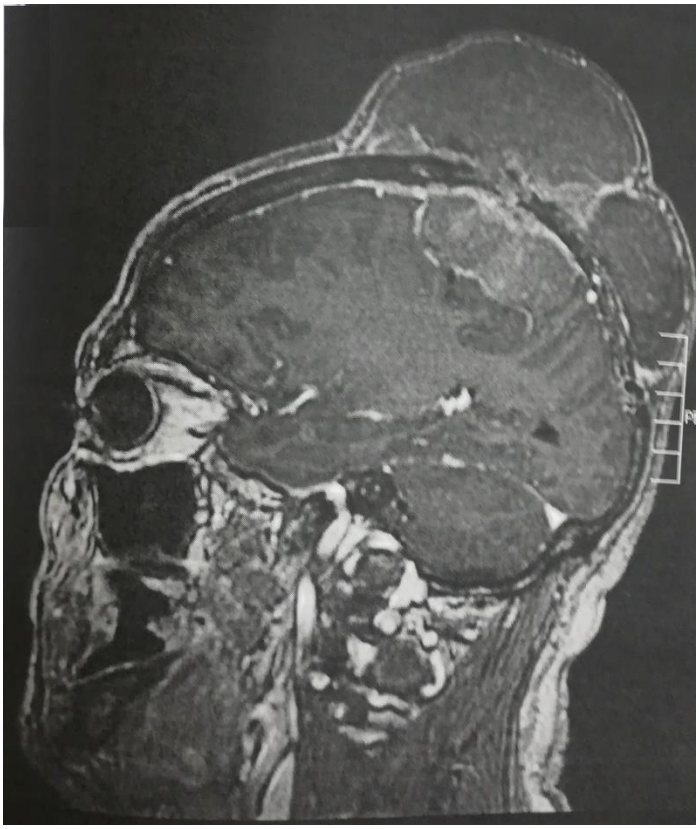


Figure 9. Pre-operative MRI of a 62-year-old male with an anaplastic meningioma with a large extracranial component. At the time of his presentation, he said he had “two cysts” in his head since two years ago and that he had not yet had the opportunity to have them removed. He had also been feeling intense headaches since that time.

- The female patient mentioned in the first line of Table 10 went from atypical meningioma diagnosis to an anaplastic one, which then recurred again (twice) as an “atypical” meningioma (this woman also had meningiomatosis). Although the reason for this “regression” in WHO grade could be attributed perhaps to an insufficient area of tissue examined, the fact that this anaplastic meningioma recurred twice as an atypical one points to another possible explanation. In fact, the “niche” where most malignant cells were located might have been removed in this patient’s third surgery, and the remaining tumor cell population that later led to a tumor recurrence was indeed that of an atypical (WHO grade II) meningioma.

Limitations of this study

There are several limitations in our study, including a small number of patients and the fact that the study is retrospective in nature. This study was also done at a single institution which meant a lower volume of cases than multicenter studies[20], but this also allowed us to have more uniform data as well as a reliable follow-up of patients. Also, patients were diagnosed over a wide range of years, meaning possible discrepancies in treatment regimens between different patients existed.

This study is also limited due to the fact that histopathological slides themselves were not reviewed, although a careful revision of each pathological report was done. Fortunately, regarding the classification of WHO grade III meningiomas, and as Champeaux et al. point out in one of the largest studies on grade III meningiomas, the definition of grade III meningioma according to the 2016 WHO Classification of Central Nervous System Tumors is practically identical to that of the 2000 and 2007 editions.[20] In 2000, mitotic count cut-offs were introduced and rhabdoid meningiomas were also categorized as grade III meningiomas. In the 1993 classification, atypical meningiomas were already classified as separate entities from those with clearly anaplastic nature.[40] The only clear differences were that, in 1993, rhabdoid meningiomas were not yet considered grade III meningiomas (nor were even considered as a meningioma subtype) and papillary meningiomas could either be classified as grade II or grade III meningiomas.[14] Given the fact that the first case in our series was diagnosed in the second half of 2000 and was already recognized as a rhabdoid meningioma, we could confirm that the 2000 WHO Classification of Tumors of the Nervous System was already used at the time.

Perhaps one of the biggest drawbacks in this study was the impossibility of confirming the exact cause of death of these patients, even though records were scrutinized for indications

of potential comorbidities or emergency room visits that might raise the suspicion for an alternative cause of death. We did find a medical report for the patient of our illustrative case (rhabdoid meningioma), certifying that he had died from a cardiopulmonary arrest after the tumor had started to invade the brainstem (thus being considered a tumor-related death). Although they only included a small number of grade III meningioma patients in their study about the real cause of death in patients with meningiomas, De Almeida et al. reported that 94.1% of high-grade (WHO grades II and III) meningioma patients died of tumor-related deaths, and all 4 grade III meningioma patients died because of their malignancy.[41] Unfortunately, for such an aggressive tumor, its short survival may make it more likely that these patients do indeed die because of their tumor and not some unrelated cause. Still, one should also take into account that, in general, the mean age at diagnosis of high-grade meningiomas seems to be higher than that for grade I meningiomas[42], and therefore people who were diagnosed with GIII meningioma may already be expected to have shorter survivals than those diagnosed with benign meningiomas.

In our study, we did not analyze specific mutations present in WHO grade III meningiomas. In terms of possible familial genetic inheritance, and to our knowledge, none of the patients who presented at our academic medical center in Coimbra were related in familial terms.

Moreover, the proportion of patients with grade II meningioma that progress to a grade III meningioma was not analyzed in our study, as we were not able to examine all grade II meningioma patients' records and follow their possible malignant transformation.

Due to the retrospective nature of our study and the advanced age of many of the patients, we are not able to fully ascertain whether some of these older patients had a childhood history of radiotherapy (especially if cranial) in order to assess possible risk factors for meningiomas.

Finally, the Coimbra University Hospital Center has not, until the date of this study, completely transitioned to an electronic medical record (EMR) system, and handwritten notes were sometimes difficult to interpret.

Advances brought by this study

Although this article refers to a small number of cases, the number is considerable when taking into account the rarity of these tumors. We also looked briefly at the psychological impact of a WHO grade III diagnosis. Even though patients in our series did not undergo a systematic psychiatric evaluation (hence the prevalence of depressive symptoms may be even higher), roughly a quarter of them already displayed signs of depression due to their diagnosis. In fact, in the case of grade III meningiomas, although not having an expected survival as short as

that for glioblastomas (whose median overall survival was estimated to be 13.5 months in a recent systematic review[43]), patients fare much worse in terms of morbidity than the majority of meningiomas patients do, which may potentiate depression and denial of illness. We are also not aware of many case series of WHO grade III meningiomas which have provided information on the temporal distribution of their cases as we did, but we would find it interesting to see if a similar trend is found in other countries of the world. We also hope to provide an example for future studies while providing clearer definitions of terms (such as “follow-up”) and by giving details on the various treatments that our patients underwent. Our study is also one of the few focusing on WHO grade III meningiomas in Southwestern Europe, where studies on these types of tumors are scarce.

Conclusion

Unfortunately, despite all attempts at improving treatment options (namely in the field of radiotherapy), prognosis for grade III meningiomas seems to have shown no substantial improvement when compared to more than two decades ago (even when considering changes in the grading of meningiomas).[44] World Health Organization Grade III meningiomas still portend a devastating prognosis and there is a pressing need to find a therapeutic regimen that can provide better clinical outcomes for these patients. Our study showed that there was a trend toward improved overall survival with gross total resection when compared to subtotal resection in these meningiomas, and that adjuvant radiotherapy significantly improved overall survival in the case of subtotally resected grade III meningiomas, but not in the gross totally resected subgroup.

Acknowledgments:

We would like to thank Dr. Olinda Rebelo for her kind help in retrieving the neuropathology reports.

Declarations of interest: None.

Funding sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. *Neuro Oncol.* 2019;21(Supplement_5): v1-v100. https://doi.org/10.1093/neuonc/noz150.
2. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, (eds.). *WHO Classification of Tumours of the Central Nervous System.* Revised 4th ed. Lyon, France: IARC; 2016.
3. Peyre M, Gauchotte G, Giry M, et al. De novo and secondary anaplastic meningiomas: a study of clinical and histomolecular prognostic factors. *Neuro Oncol.* 2018;20(8): 1113-1121. https://doi.org/10.1093/neuonc/nox231.
4. Zhu H, Xie Q, Zhou Y, et al. Analysis of prognostic factors and treatment of anaplastic meningioma in China. *J Clin Neurosci.* 2015;22(4): 690-695. https://doi.org/10.1016/j.jocn.2014.10.023.
5. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma. With particular reference to bronchogenic carcinoma. 1948;1(4): 634-656.
6. Simpson D. The recurrence of intracranial meningiomas after surgical treatment. *J Neurol Neurosurg Psychiatry.* 1957;20(1): 22-39. https://doi.org/10.1136/jnnp.20.1.22.
7. Cardoso FS. Liver transplantation in an ICU dominated by COVID-19. *Liver Transpl.* 2020. https://doi.org/10.1002/lt.25770.
8. Balasubramanian SK, Sharma M, Silva D, et al. Longitudinal experience with WHO Grade III (anaplastic) meningiomas at a single institution. *J Neurooncol.* 2017;131(3): 555-563. https://doi.org/10.1007/s11060-016-2321-8.
9. Lim YS, Kim MK, Park BJ, Kim TS, Lim YJ. Long term clinical outcomes of malignant meningiomas. *Brain Tumor Res Treat.* 2013;1(2): 85-90. https://doi.org/10.14791/btrt.2013.1.2.85.
10. Brem SS, Bierman PJ, Brem H, et al. Central nervous system cancers. *J Natl Compr Canc Netw.* 2011;9(4): 352-400. https://doi.org/10.6004/jnccn.2011.0036.
11. Pinto CS, Anderson RN, Martins H, Marques C, Maia C, do Carmo Borralho M. Mortality Information System in Portugal: transition to e-death certification. *Eurohealth.* 2016;22(2): 1-53.
12. Association WM. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* 2013;310(20): 2191-2194. https://doi.org/10.1001/jama.2013.281053.

13. Al-Mefty O, Kadri PA, Pravdenkova S, Sawyer JR, Stangeby C, Husain M. Malignant progression in meningioma: documentation of a series and analysis of cytogenetic findings. *J Neurosurg.* 2004;101(2): 210-218. https://doi.org/10.3171/jns.2004.101.2.0210.

14. Kleihues P, Burger PC, Scheithauer BW. *Histological Typing of Tumours of the Central Nervous System.* Second ed. Berlin, Heidelberg: Springer Berlin Heidelberg; 1993.

15. Claus EB, Walsh KM, Calvocoressi L, et al. Cigarette smoking and risk of meningioma: the effect of gender. *Cancer Epidemiol Biomarkers Prev.* 2012;21(6): 943-950. https://doi.org/10.1158/1055-9965.EPI-11-1059.

16. Wiemels JL, Wrensch M, Sison JD, et al. Reduced allergy and immunoglobulin E among adults with intracranial meningioma compared to controls. *Int J Cancer.* 2011;129(8): 1932-1939. https://doi.org/10.1002/ijc.25858.

17. DeMonte F, McDermott MW, Al-Mefty O. *Al-Mefty's meningiomas.* 2nd ed. New York: Thieme; 2011.

18. Arnautović KI, Al-Mefty O, Husain M. Ventral foramen magnum meninigiomas. *J Neurosurg.* 2000;92(1 Suppl): 71-80. https://doi.org/10.3171/spi.2000.92.1.0071.

19. Sun SQ, Hawasli AH, Huang J, Chicoine MR, Kim AH. An evidence-based treatment algorithm for the management of WHO Grade II and III meningiomas. *Neurosurg Focus.* 2015;38(3): E3. https://doi.org/10.3171/2015.1.FOCUS14757.

20. Champeaux C, Jecko V, Houston D, et al. Malignant Meningioma: An International Multicentre Retrospective Study. *Neurosurgery.* 2019;85(3): E461-E469. https://doi.org/10.1093/neuros/nyy610.

21. Zhang GJ, Zhang GB, Zhang YS, et al. World Health Organization Grade III (Nonanaplastic) Meningioma: Experience in a Series of 23 Cases. *World Neurosurg.* 2018;112: e754-e762. https://doi.org/10.1016/j.wneu.2018.01.149.

22. Zhang GJ, Zhang YS, Zhang GB, et al. Prognostic factors and the management of anaplastic meningioma. *Clin Neurol Neurosurg.* 2018;170: 13-19. https://doi.org/10.1016/j.clineuro.2018.03.028.

23. Yu JS, Yong WH, Wilson D, Black KL. Glioblastoma induction after radiosurgery for meningioma. *Lancet.* 2000;356(9241): 1576-1577. https://doi.org/10.1016/S0140-6736(00)03134-2.

24. Lee HS, Kim JH, Lee JI. Glioblastoma following radiosurgery for meningioma. *J Korean Neurosurg Soc.* 2012;51(2): 98-101. https://doi.org/10.3340/jkns.2012.51.2.98.

25. Masalha W, Heiland DH, Delev D, et al. Survival and Prognostic Predictors of Anaplastic Meningiomas. *World Neurosurg.* 2019;131: e321-e328. https://doi.org/10.1016/j.wneu.2019.07.148.

26. Maier AD, Bartek J, Eriksson F, et al. Clinical and histopathological predictors of outcome in malignant meningioma. *Neurosurg Rev.* 2019. https://doi.org/10.1007/s10143-019-01093-5.

27. Moliterno J, Cope WP, Vartanian ED, et al. Survival in patients treated for anaplastic meningioma. *J Neurosurg.* 2015;123(1): 23-30. https://doi.org/10.3171/2014.10.JNS14502.

28. Wang XQ, Chen H, Zhao L, et al. Intracranial papillary meningioma: a clinicopathologic study of 30 cases at a single institution. *Neurosurgery.* 2013;73(5): 777-790; discussion 789. https://doi.org/10.1227/NEU.0000000000000133.

29. Sughrue ME, Sanai N, Shangari G, Parsa AT, Berger MS, McDermott MW. Outcome and survival following primary and repeat surgery for World Health Organization Grade III meningiomas. *J Neurosurg.* 2010;113(2): 202-209. https://doi.org/10.3171/2010.1.JNS091114.

30. Goldbrunner R, Minniti G, Preusser M, et al. EANO guidelines for the diagnosis and treatment of meningiomas. *Lancet Oncol.* 2016;17(9): e383-391. https://doi.org/10.1016/S1470-2045(16)30321-7.

31. Sade B, Chahlavi A, Krishnaney A, Nagel S, Choi E, Lee JH. World Health Organization Grades II and III meningiomas are rare in the cranial base and spine. *Neurosurgery.* 2007;61(6): 1194-1198; discussion 1198. https://doi.org/10.1227/01.neu.0000306097.38141.65.

32. Cornelius JF, Slotty PJ, Steiger HJ, Hänggi D, Polivka M, George B. Malignant potential of skull base versus non-skull base meningiomas: clinical series of 1,663 cases. *Acta Neurochir (Wien).* 2013;155(3): 407-413. https://doi.org/10.1007/s00701-012-1611-y.

33. Kane AJ, Sughrue ME, Rutkowski MJ, et al. Anatomic location is a risk factor for atypical and malignant meningiomas. *Cancer.* 2011;117(6): 1272-1278. https://doi.org/10.1002/cncr.25591.

34. Liang RF, Xiu YJ, Wang X, et al. The potential risk factors for atypical and anaplastic meningiomas: clinical series of 1,239 cases. *Int J Clin Exp Med.* 2014;7(12): 5696-5700.

35. Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. *J Neurooncol.* 2010;99(3): 307-314. https://doi.org/10.1007/s11060-010-0386-3.

36. Bi WL, Zhang M, Wu WW, Mei Y, Dunn IF. Meningioma Genomics: Diagnostic, Prognostic, and Therapeutic Applications. *Front Surg.* 2016;3: 40. https://doi.org/10.3389/fsurg.2016.00040.

37. Scheithauer BW. Development of the WHO classification of tumors of the central nervous system: a historical perspective. *Brain Pathol.* 2009;19(4): 551-564. https://doi.org/10.1111/j.1750-3639.2008.00192.x.

38. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol.* 2016;131(6): 803-820. https://doi.org/10.1007/s00401-016-1545-1.

39. Kochanski RB, Byrne N, Arvanitis L, Bhabad S, Byrne RW. A rare intracranial tumor consisting of malignant anaplastic and papillary meningioma subtypes. *Surg Neurol Int.* 2016;7: 21. https://doi.org/10.4103/2152-7806.176674.

40. Burger PC. Revising the World Health Organization (WHO) Blue Book--'Histological typing of tumours of the central nervous system'. *J Neurooncol.* 1995;24(1): 3-7. https://doi.org/10.1007/bf01052650.

41. de Almeida AN, Pereira BJA, Pires Aguiar PH, et al. Clinical Outcome, Tumor Recurrence, and Causes of Death: A Long-Term Follow-Up of Surgically Treated Meningiomas. *World Neurosurg.* 2017;102: 139-143. https://doi.org/10.1016/j.wneu.2017.03.009.

42. Park JS, Sade B, Oya S, Kim CG, Lee JH. The influence of age on the histological grading of meningiomas. *Neurosurg Rev.* 2014;37(3): 425-429; discussion 429. https://doi.org/10.1007/s10143-014-0537-7.

43. Marenco-Hillembrand L, Wijesekera O, Suarez-Meade P, et al. Trends in glioblastoma: outcomes over time and type of intervention: a systematic evidence based analysis. *J Neurooncol.* 2020;147(2): 297-307. https://doi.org/10.1007/s11060-020-03451-6.

44. Palma L, Celli P, Franco C, Cervoni L, Cantore G. Long-term prognosis for atypical and malignant meningiomas: a study of 71 surgical cases. *J Neurosurg.* 1997;86(5): 793-800. https://doi.org/10.3171/jns.1997.86.5.0793.

Appendix I – CHUC Ethics Committee Approval

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

CHUC CENTRO HOSPITALAR E UNIVERSITÁRIO DE COIMBRA

Comissão de Ética para a Saúde

Prof.ª Doutora Helena Sá
Adjunta do Diretor Clínico
Visto CHUC - EPE
para difusão

27/3/20

Exmo. Senhor
Dr. Francisco Parente
Digmº Diretor Clínico do CHUC

SUA REFERÊNCIA	SUA COMUNICAÇÃO DE	NOSSA REFERÊNCIA	DATA
		N.º 062/CES	25-03-2020

Proc. N.º **CHUC-017-20**

Estudo Observacional: "**MENINGIOMAS GRAU III (ORGANIZAÇÃO MUNDIAL DE SAÚDE): ANÁLISE RETROSPETIVA NUM CENTRO HOSPITALAR UNIVERSITÁRIO**"
Entrada na CES: 11-02-2020
Visto na Reunião de: 26-02-2020 (**Parecer Desfavorável, Ofº053/19)**
Reentrada na CES: 11-03-2020
Investigador/a/es: Maria Eduarda Carvalho Lucas de Sá Marta, Estudante de Mestrado Integrado em Medicina **Coordenador**: José Luís Monteiro Alves, Prof. Assit Convidado de Neurocirurgia **Co-Investigador**: Marcos Daniel De Brito Da Silva Barbosa, Prof. Auxiliar de Neurocirurgia
Serviço de Realização: Neurocirurgia – Centro Hospitalar e Universitário de Coimbra

Cumpre informar Vossa Ex.ª que a CES - Comissão de Ética para a Saúde do Centro Hospitalar e Universitário de Coimbra, reunida em 25 de março de 2020, considera que se encontram respeitados os requisitos éticos adequados à realização do estudo, bem como à dispensa de Consentimento Informado, pelo que emite parecer favorável ao seu desenvolvimento no CHUC.

Mais se informa que a CES do CHUC deverá ser semestralmente atualizada em relação ao desenvolvimento dos estudos favoravelmente analisados e informada da data da conclusão dos mesmos, com envio de relatório final.

Com os melhores cumprimentos,

A Comissão de Ética para a Saúde do CHUC, E.P.E.

Prof. Doutor João Pedroso de Lima
Presidente

CES do CHUC: Prof. Doutor João Pedroso de Lima, Prof. Doutora Margarida Silvestre, Enfª Adélio Tinoco Mendes, Dra. Cláudia Santos, Dra. Isabel Ventura, Dr. José António Feio, Rev. Pe. Doutor Nuno dos Santos, Dr. Pedro Lopes, Dra. Teresa Monteiro

Centro Hospitalar e Universitário de Coimbra
Praceta Prof. Mota Pinto, 3000 - 075 Coimbra, PORTUGAL
TEL + 351 239 400 408 – **FAX** + 351 239 405 646 – **EMAIL** secetica@chuc.min-saude.pt – **www.chuc.min-saude.pt**

1/1