Resumo

O termo meningioma foi utilizado pela primeira vez por Harvey Cushing em 1922, para descrever tumores com origem nas meninges do cérebro e da coluna vertebral. O vasto espectro de apresentação clínica e do prognóstico deste tipo de tumores é reconhecido desde 1938, quando foram descritas variantes associadas a sobrevivências inferiores a 2.5 anos.[1,2] Apesar do progresso alcançado com novas técnicas de diagnóstico, classificação histológica, técnicas cirúrgicas melhoradas e terapêuticas adjuvantes, o tratamento contemporâneo do meningioma ainda não inclui linhas orientadoras reconhecidas a nível internacional. De facto, as opções terapêuticas para este tipo de doentes, especialmente a recomendação de radioterapia adjuvante no meningioma atípico é um dos tópicos mais discutidos desta área.[3] Por este motivo, a análise de fatores prognósticos associados a uma maior taxa de recorrência do tumor, morbilidade e mortalidade é vital para selecionar os doentes que poderão beneficiar de um plano de tratamento mais agressivo. Este estudo teve como objetivo realizar uma análise descritiva do tratamento de meningiomas atípicos num centro neurocirúrgico terciário. Adicionalmente, analisou o impacto dos fatores relacionados com a cirurgia, terapêutica adjuvante, histologia e com a história do doente na sobrevivência livre de doença (SLD) e na sobrevivência total (ST). Os resultados obtidos estão de acordo com a literatura existente e confirmam a importância da resseção total (RT) na SLD. Aos 5 anos após a cirurgia, os doentes que foram submetidos a resseção subtotal (RS) registavam uma SLD de 35.7%, aproximadamente metade da registada pelos doentes com RT (SLD de 68.8%, log-rank:0.047, Breslow:0.033). Parece existir um efeito benéfico associado à radioterapia adjuvante nos doentes com RS, tendo estes registado uma SLD aos 5 anos de 66.7%, comparada com valores de 29.3% nos doentes que não receberam terapêutica adjuvante (log-rank:0.262, Breslow: 0.122). Esta associação não foi observada para o grupo de doentes submetidos a RT. A análise do grupo que manifestou recidiva tumoral identificou como fatores de risco a idade (p=0.033), história de meningioma atípico prévio (p=0.012), cirurgia cerebral prévia (p=0.014), invasão dos seios venosos e do córtex (p=0.018 e p=0.002), RS (p=0.009) e graus elevados de edema (p=0.041). Os resultados deste estudo corroboram a abordagem cirúrgica com o intuito de RT como objetivo primário no tratamento do meningioma atípico. Caso a resseção tumoral máxima não seja possível deverá ser considerado o uso de radioterapia adjuvante. O papel desta terapêutica adjuvante após RT mantem-se controverso.

Palavras-chave: meningioma atípico, extensão da resseção, radioterapia adjuvante.

Abstract

The term meningioma was coined in 1922 by Harvey Cushing to describe masses arising in the meninges of the brain and spinal cord. The wide spectrum of presentation and clinical outcome of these tumours has been recognized from as early as 1938, when variants associated with survival rates of 2.5 years were described.[1,2] Despite the progress in diagnostic techniques, histological classification, new surgical approaches and adjuvant therapies, the contemporary management of meningioma patients still lacks clear and internationally validated guidelines. In fact the treatment options for these patients, particularly the use of adjuvant radiotherapy in atypical meningioma (AM), remains one of the most discussed topics in this area.[3] For this reason, the study of prognostic factors associated with increased tumour recurrence, morbidity and mortality is vital for selecting patients who may benefit from an aggressive treatment plan from those who are not likely to. This study aimed to provide a descriptive analysis of the treatment of atypical meningioma at a tertiary neurosurgical centre. Furthermore, it evaluated the impact of the surgical outcome and adjuvant treatment as well as the histological and patients' related factors in progression free survival (PFS) and overall survival (OS). The results obtained are consistent with the existing literature and confirm the importance of gross total resection (GTR) for improved progression free survival. The 5 year PFS for the patients who received subtotal resection (STR) was 35.7%, which was approximately half of the values registered for patients who received GTR surgeries (5 year PFS of 68.8%; log-rank of 0.047 and Breslow of 0.033). There seems to be a benefit in recommending adjuvant radiotherapy in patients who underwent STR, with a 5 year PFS of 66.7% in this group compared with 29.3% in the STR only group (log-rank of 0.262 and Breslow of 0.122). This association was not seen for GTR patients. The analysis of the recurrence group identified older age (p=0.033), previous grade II meningioma (p=0.012), previous brain surgery (p=0.014), venous sinus and cortex invasion (p=0.018 and p=0.002), STR (p=0.009) and higher grades of oedema (p=0.041) as recurrence risk factors. The evidence from this study supports GTR as a primary goal in the management of atypical meningioma patients. If safe maximal resection in not possible adjuvant radiotherapy should be considered. The role of this adjuvant treatment following GTR remains controversial.

Key words: atypical meningioma, extent of resection, adjuvant radiotherapy

Contents

List of abbreviations and units

AM – atypical meningioma
cm – centimetre
CNS – central nervous system
CSF – cerebralspinal fluid
CT – computerized tomography
EBRT – external beam radiation therapy
e.g. – exempli gratia
EOR – extent of resection
EORTC - European Organisation for Research and Treatment of Cancer
GTR – gross total resection
Gy - Gray
HPF – high power fields
MRI – magnetic resonance imaging
OS – overall survival
PFS – progression free survival
ROAM - Radiotherapy versus Observation following surgical resection of Atypical Meningioma
SRS – stereotactic radiosurgery
STR – subtotal resection
UK – United Kingdom
WHO – World Health Organization

I. Introduction

Meningiomas are the most frequently diagnosed primary central nervous system (CNS) tumours in adults, comprising approximately one third of all cases.[4] They are more common in women than in men and they particularly affect middle aged and elderly patients.[5] Even though the majority of the cases are sporadic, meningiomas may also be present in hereditary syndromes, from which the best documented is neurofibromatosis type 2. Recognized and suggested risk factors include radiation exposure, sexual hormones, head trauma, familiar history of benign brain tumours and occupational and dietary causes.[6–8] These tumours originate in the arachnoid cap cells that assemble the outer layer of the arachnoid mater and the arachnoid villi, being in 90% of the cases intracranial. The vast majority are located in the falx and parasagittal region (25%), in the convexity (19%) and along the sphenoid ridge (17%). Other common locations are the suprasellar region (9%), the olfactory groove (8%), the posterior fossa (8%) and the middle fossa (4%). Less frequently meningiomas can be found in the peri-torcular region, in the lateral ventricles, in the foramen magnum and in the orbit or optic nerve sheath.[9]

Most symptoms are insidious, depending on the tumour location and resulting from the compression of adjacent structures. Thus, the presentation can range from easily recognizable signs and symptoms such as headache, seizure, paresis or visual field deficits to more subjective alterations, for instance personality disorders.[10,11] Magnetic Resonance Imaging (MRI) and Computer Tomography (CT) with the application of contrast medium are the methods of choice for the neuroradiological evaluation of the tumour (Figure 1).[12]

As a group, meningiomas show more histological variants than any other tumour and although its classification is complex, it assumes a pivotal role in the disease management. The World Health Organization (WHO) classification of central nervous system tumours, divides meningiomas into three grades: grade I (benign), grade II (atypical) and grade III (malignant)/(Figure 2).[13,14] Atypical meningiomas represent 5 to 15% of all meningiomas, with the histological subgroups “atypical”, “chordoid” and “clear cell” in descending frequency. In general, atypical meningiomas are associated with higher recurrence rates (30-40%) and increased morbidity and mortality compared to benign meningiomas.[15]

Currently the treatment options for atypical meningioma remain controversial. The range includes watchful waiting, surgery, stereotactic radiosurgery (SRS), radiotherapy (more recently ion beam radiotherapy) and combinations thereof. Chemotherapy and other

biologic therapies are reserved for selected cases.[1] Total surgical resection of the tumour and invaded structures is the current gold standard, however, this is not always anatomically possible, especially for tumours located in the skull base.[16] The extent of the surgical resection can be classified according to the Simpson grading system, proposed by Donald Simpson in 1957. Similarly to histological grading, this classification is also a risk stratification method that correlates closely with recurrence.[17]

Regarding radiotherapy, there is no consensus on recommendation as a standard adjuvant therapy to surgery in atypical meningioma, particularly after GTR. Authors have suggested that the use of radiotherapy immediately after surgical resection could decrease the recurrence rate and thus result in a better outcome. Recent meta-analysis and systematic reviews have revealed that this might be correct for the local control of the disease, particularly in cases of subtotal resection, however there is no impact in overall survival.[1,18–20] Although the side-effects of radiotherapy have decreased in the last decades, they are still responsible for considerable morbidity (3.4-16.7% of AM patients) and consequently the risk-benefit ratio should be carefully considered.[20]

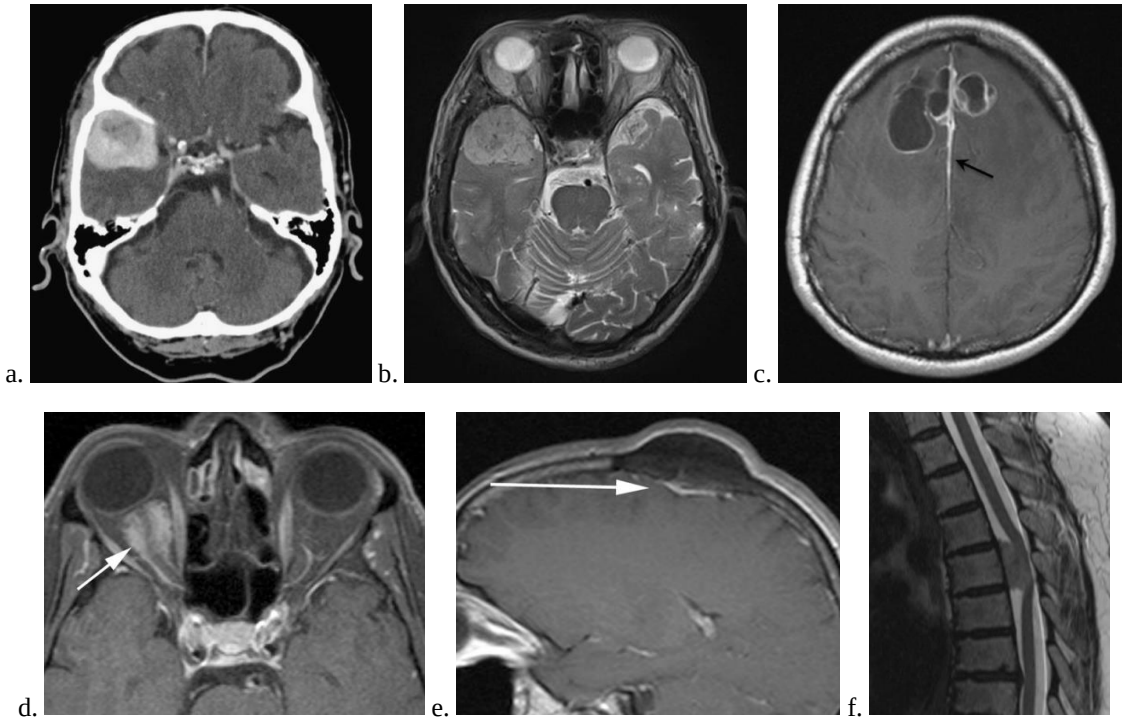

Figure 1 –Meningioma imaging with CT scan and MRI. a. sphenoid ridge meningioma on CT scan (axial); b. same lesion on T2 MRI (axial); c. cystic meningioma with dura tail (black arrow) on T1 MRI (axial); d. meningioma surrounding the right optic nerve on T1 MRI (axial) ; e. *en plaque* meningioma with hyperostotic focus on T1 MRI (sagittal); f. spinal cord meningioma at the T5 level narrowing the spinal canal on T2 MRI (sagittal) / (images from[12,21])

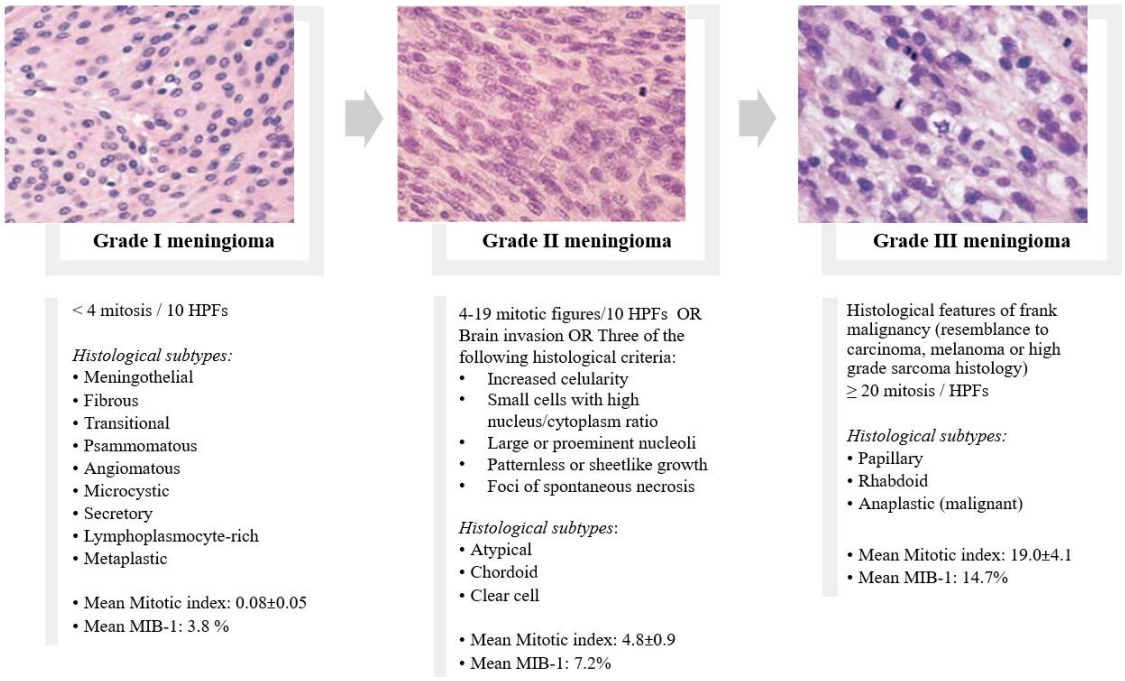

Figure 2: WHO 2007 Meningioma grading system. The histological images correspond to meningothelial (grade I), atypical (grade II) and anaplastic tumours (grade III). In immunochemistry analysis all grades of meningioma are positive for vimentin stain, grade I meningiomas are more commonly positive for epithelial membrane antigen (EMA) stain and secretory meningiomas are positive for carcinoembryonic antigen (CEA) stain (adapted from[8,22,23]).

II. Aims of the Study

The main problem for the current management of meningioma, particularly atypical meningioma, is to predict which patients are more prone to recurrence.[24] The identification of prognostic factors is of vital importance since these allow recognizing which patients benefit from a more aggressive treatment plan or require a closer follow up. One of the main discussed topics in meningioma management is related to the recommendation of radiotherapy in atypical meningioma following GTR or STR and its role in prevention of recurrence.

This study aims to retrospectively analyse the management of patients with atypical meningiomas at a tertiary neurosurgical centre and to determine the impact of surgical, histological, adjuvant treatment and patient related factors in the progression of the disease.

III. Methods

Patient selection

This retrospective cohort study includes the analysis of all grade II meningioma patients who underwent surgery at the Neurosurgery Department of the General Hospital of Vienna in a period of 12 years (January 2002 to December 2013). To evaluate the impact of previous treatments on tumour progression and clinical outcome, we included primary and recurrent atypical meningiomas, as well as recurrent grade II meningiomas after grade I meningioma. Other inclusion criteria were the patients' age at the time of the surgery (≥18 years) and the existence of a neuropathology report confirming the grade II histology according to the WHO 2000 or 2007 diagnostic criteria.

Source of information and study approval

All required information was retrieved from the patients' clinical files, surgical reports, histological reports, discharge letters and neuroradiology images stored at the Neurosurgery Department at the Medical University of Vienna. For confidentiality purposes, patient data was anonymized and only authorized personnel had access to the original files. The ethics committee from this institution approved this study, which was performed according to the standards of the Declaration of Helsinki.

Variables assessed

The data gathered for each patient included age, gender, previous grade I or grade II meningioma, previous brain surgery, neurofibromatosis type 2 diagnosis, radiation exposure history and existing comorbidities. Due to the highly variable location of meningiomas and their broad range of clinical manifestations, several features were considered for the presenting signs and symptoms, notably: headache, pain, vertigo, paresis, sensibility disorder, visual impairment, hearing deficit, disturbance of taste or smell, exophthalmus, swelling, seizure, aphasia, change of personality, disturbance of consciousness and neurogenic bowel and/or bladder dysfunction.

The location, number, diameter (in cm) of the tumour and the presence of perifocal oedema was obtained from the neuroradiology images and/or from the surgical report. The exact location of the tumours was categorized into the following groups: spinal,

convexity, falx, tentorium, sphenoid or sphenoorbital, orbital, olfactory, frontobasal, parasagittal, petroclival or clival, falcotentorial, intraventricular, middle fossa floor, cerebellar falx or multiple. In order to facilitate the statistical analysis, these locations were further grouped into convexity/falx/tentorium, skull base, spinal, intraventricular and multiple. In cases of multiple tumours, the size of the biggest tumour was preferred. The presence of oedema was semiquantitatively classified into grades: mild, moderate and severe.

The analysis of the surgical treatment included the assessment of invasion of adjacent structures such as bone, venous sinus, arachnoid layer and/or cortex. The Simpson classification was also reassessed and subdivided into gross total resection (GTR – Simpson grades I and II) and subtotal resection (STR – Simpson III and IV) / (Figure 3).[25]

For the histological analysis, tumours were subcategorized according to the WHO 2000 and 2007 classification into atypical, chordoid and clear cell. From these histological reports the MIB-1 number (Ki-67 index) and mitotic index (number of mitosis per 10 high power fields) was also recorded when present.

The length of hospitalization and the peri-operative complications were also studied. The latter were subclassified into infection, CNS haemorrhage, non-CNS haemorrhage, CNS ischaemia, non-CNS ischaemia, ventricular system disorder, neurologic deficit, psychiatric disorder and death. The Clavien Dindo complication scale was also used.[26]

The adjuvant therapies after primary surgery included external beam radiation therapy (EBRT) and chemotherapy and for these we noted the start date, the radiation dose and the chemotherapy scheme.

During the follow up we noted tumour recurrence with the following characteristics: clinical presentation, location, size, type of meningioma spread (local and cerebrospinal fluid (CSF) spread), treatment type and histological grade. Recurrence was defined as the date at which the patient received treatment for the recurrent tumour or in cases of watchful waiting the date of the neuroradiology diagnosis of the recurrent tumour. Treatment options for the recurrent meningioma included surgery, SRS, EBRT, chemotherapy (with Imatinib, Glivec®) or any combination of these. Finally, a status variable was assigned to each patient as stable, progressing, meningioma related death, non-meningioma related death or unknown cause of death.

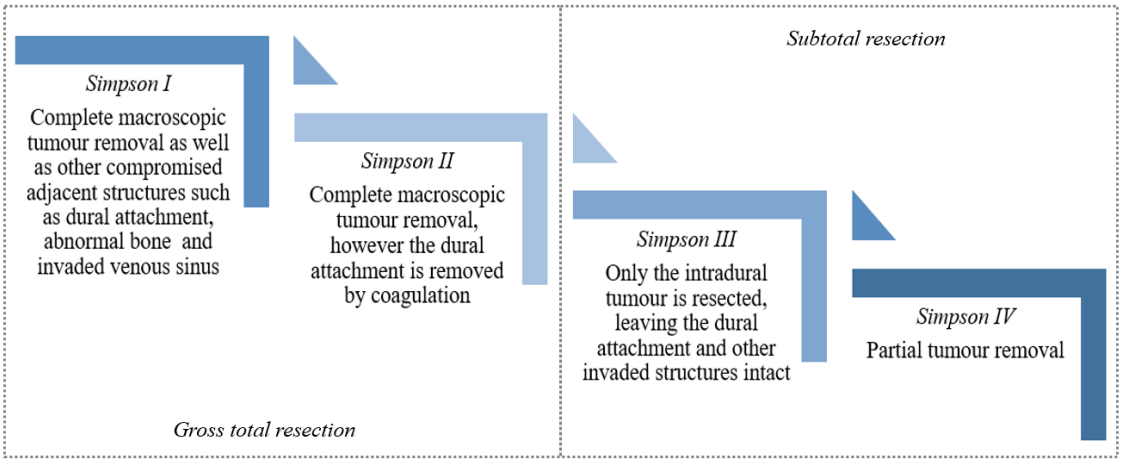

Figure 3 – Simpson resection grades and division according to gross total resection (Simpson I and II) and subtotal resection (Simpson III and IV)

Statistical analysis

The primary question of this study was to test if there was a difference in overall and progression-free survival grouped by specific parameters. Kaplan-Meier curves based on the extent of resection were used for this purpose together with log rank and Breslow tests. Additionally, the same calculations were done for GTR and STR according to the fact whether patients received postoperative radiotherapy or not. Quantitative variables were assessed for normality with Shapiro-Wilk tests. Comparisons between groups were then performed with Student test and Mann Whitney test, as applicable. The association between categorical variables was assessed resorting to Chi-square-tests or Fischer exact tests, resorting to Monte Carlo simulations when needed.[27] The statistical analysis was performed using IBM® SPSS® Software version 22. The level of significance adopted was α=0.05.

IV. Results

Patient and tumour characteristics

Of 140 patients that met the inclusion criteria of this study, 62% were female and 38% were male, with a mean age at the surgical intervention of 56 years (range 18 to 82 years). Of those, 18.7% harboured recurrent meningiomas (10.1% had previous grade I meningioma, 7.2% had previous grade II meningioma and 1.4% had both previous grade I and II meningiomas). Overall, 22.1% received previous brain surgery at some point of their life, 7.1% had a history of radiation exposure and only one patient had a confirmed diagnosis of neurofibromatosis type 2. The most frequently encountered comorbidities were cardiovascular and metabolic (e.g. diabetes and dyslipidaemia), followed by thrombotic, oncologic, psychiatric and neurologic disorders (Table 1 appendix).

The majority of patients was symptomatic (88.6%) and the most common symptoms were headache (39%), visual impairment (29%), paresis (22%) and seizures (22%) / (Table 2 appendix). The mean diameter of the meningiomas was 4.18±1.92 cm (range 1.00 to 9.00 cm). Preferential locations were sphenoid or sphenoorbital (24.5%), convexity (21.6%), parasagittal (17.3%) and falx (8.6%). Multiple meningiomas were found in 10% of cases and the presence of oedema was verified in 50% of the cases.

The main histological subgroup was atypical (84.3%), followed by the chordoid and clear cell variants in 12.9% and 2.9% of the cases respectively. The mitotic index, when available, was ≥5 in 83% of the cases and it was ≥8 in 10% of the cases. The MIB-1 number was obtained for 40 cases, with a mean value of 13.14±5.42% (range 4.2 to 28.0%) / (Table 3 appendix).

Treatment characteristics

Gross total resection (Simpson grades I and II) was achieved in 78% of the cases. Adjacent structure invasion was a frequent finding with 59.3% of the tumours invading the arachnoid, 28.6% the cortex, 25.0% the bone and 17.9% a venous sinus.

The mean hospital stay was 15±13.27 days (range 4 - 138 days), with a complication rate of 21%, the majority being related to neurological disorders (e.g. hemiparesis, aphasia, vision-field deficits, Jacksonian seizures), ventricular system disorders (e.g. CSF fistula and hydrocephalus) and CNS haemorrhage. During the hospital stay two of these patients died due to severe brain oedema and haemorrhage (Table 4 appendix).

External beam radiation therapy (EBRT) was given to 10% of the patients with a mean dose of 55±9.59 Gy (range 24.0-60.0 Gy). One patient received adjuvant chemotherapy with Imatinib (Glivec®). No complications following adjuvant treatment were noted.

Recurrence and follow up characteristics

For this part of the study, 24 patients with no follow up were excluded, as well as the 2 patients who died during the primary hospital stay. From these patients 26.3% had tumour recurrence during the follow up, with 16.7% registering one tumour recurrence and 9.6% presenting more than one tumour recurrence. At recurrence, the majority of the cases were asymptomatic (60%) and the mean tumour diameter was 2.82±1.36 cm (range 0.70-6.60). In one third of the cases there were multiple tumours. The most common locations were the convexity (13.3%) and the sphenoid or sphenoorbital regions (13.3%). In half of the cases the recurrence resulted from local spread of initial tumour, while the other half occurred due to CSF spread. Treatments of recurrent tumours included surgery, SRS, EBRT, chemotherapy, watchful waiting and combined treatment strategies (Table 5 appendix, Figure 4).

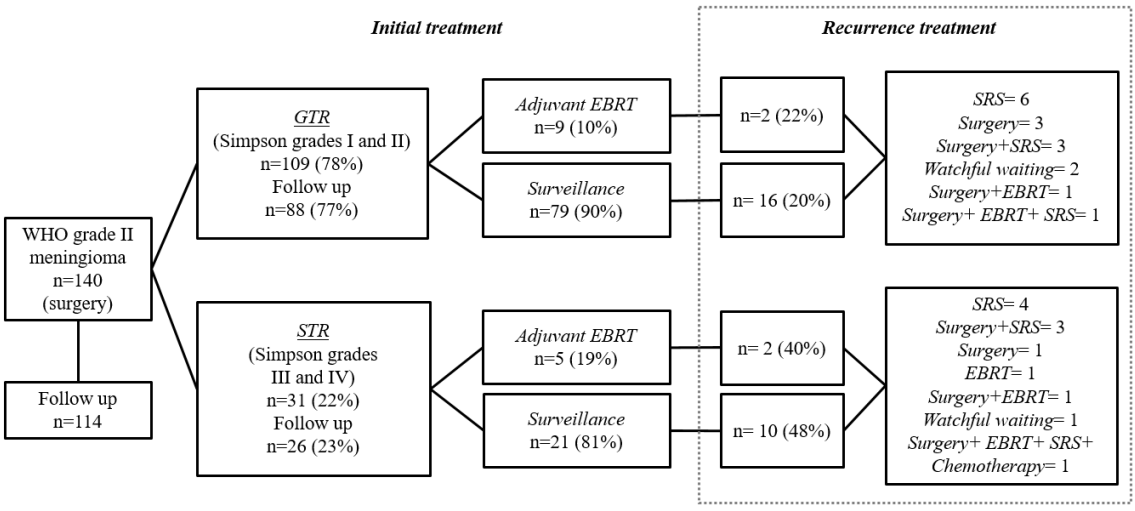

Figure 4 – Pattern of recurrence and treatment options

Regarding the patients' status at the end of the follow up period, 86.9% were stable, 3.5% were progressing and 9.6% were deceased. The cause of death was related to the meningioma in 3.5% of the cases, it was attributable to other causes in 2.6% of the cases and it was unknown in the remaining 3.5% of the patients. Three patients (10% of the recurrent tumours) underwent malignant transformation to grade III meningioma (Table 6 appendix).

Tumour precursors: primary grade II tumours and recurrent grade II tumours

We further analysed cases depending on primary grade II tumour or grade II meningioma recurrence. This analysis revealed that the recurrence group had significantly more commonly previous radiation exposure (p=0.005), was less symptomatic at presentation (p=0.033) and had more sinus and cortex invasion (p=0.024 and p=0.012). They were also more prone to recurrence (p=0.012) and they showed a higher progression rate to grade III meningiomas (p=0.029). They also seem to have a greater probability of multiple recurrence, even though this parameter did not reach statistical significance (Figure 5 and Table 1).

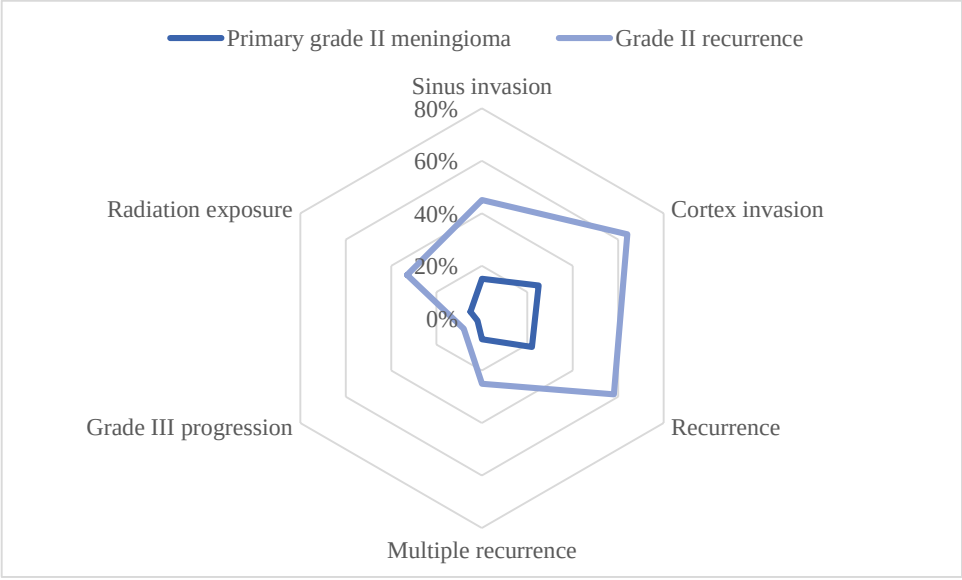

Figure 5: Comparison between primary grade II meningioma and grade II recurrence groups

Table 1: Characterization of the primary grade II and grade II meningioma recurrence groups.[a]

Variable	Primary grade II meningioma	Grade II recurrence	P-value
Female: Male	80 (63%): 47 (37%)	7 (58%): 5 (42%)	0.763
Age	55.80±13.64	58.58±12.99	0.458
Previous radiation exposure (No : Yes)	121 (95%): 6 (5%)	8 (66%): 4 (33%)	**0.005**
Diameter (cm)	4.23±1.97	3.62±0.90	0.466
Symptoms (No: Yes)	12 (9%): 115 (91%)	4 (33%): 8 (67%)	**0.033**
Skull base (No: Yes)	81 (43%): 46 (57%)	8 (67%): 4 (33%)	1.000
Histology Atypical: Chordoid: Clear cell	107 (84%): 17 (13%): 3 (3%)	10 (84%): 1 (8%): 1 (8%)	0.550
Mitotic index (<5:≥5)	17 (16%): 90 (84%)	3 (33%): 6 (66%)	0.185
Mitotic index (<8:≥8)	96 (90%): 11 (10%)	8 (89%): 1 (11%)	1.000
MIB	13.21±5.69	13.47±0.99	0.862
Bone invasion (No: Yes)	95 (75%): 32 (25%)	9 (82%): 2 (18%)	1.000
Arachnoid Invasion (No: Yes)	54 (43%): 73 (57%)	2 (18%): 9 (82%)	0.199
Sinus invasion (No: Yes)	108 (85%): 19 (15%)	6 (55%): 5 (45%)	**0.024**
Cortex invasion (No: Yes)	95 (75%): 32 (25%)	4 (36%): 7 (64%)	**0.012**
GTR:STR	100 (79%): 27 (21%)	9 (75%): 3 (25%)	0.722
Recurrence (No: Yes)	79 (78%): 22 (22%)	5 (42%): 7 (58%)	**0.012**
Multiple recurrence (No: Yes)	93 (92%): 8 (8%)	9 (75%): 3 (25%)	0.093
Grade 3 progression (No: Yes)	100 (99%): 1 (1%)	10 (83%): 2 (17%)	**0.029**

[a] Data presented as mean (±standard deviation) or as number (percentage) of patients, where applicable. The p-values included in the table were obtained with Mann-Whitney tests for age (years), diameter (cm) and MIB (%). The remaining p values were obtained with chi-square tests or Fischer exact tests.

Extent of resection

As described before GTR was achieved in 78% (109 patients) of the cohort. Since the extent of resection (EOR) is reported by several studies as one of the most important factors for increased survival, prognostic factors were further studied (Table 2).

The most important factors for the EOR were venous sinus invasion ($p<0.0001$) and tumour location ($p=0.003$ for group location and $p=0.008$ for exact location). GTR was performed in all cases of frontobasal, middle fossa floor, cerebellar falx and orbital tumours. Convexity meningiomas, which represent one of the most frequent locations, were also completely excised in the great majority of the cases (97%). High rates of GTR were also observed for petroclival and clival (86%) sphenoid and sphenoorbital (85%), falx (75%), multiple (75%), parasagittal (66%) and olfactory (66%) meningiomas.

The least successful locations were registered for falcotentorial, spinal, intraventricular and tentorial meningiomas. Other factors that seem to influence the extent of resection are previous surgery and previous radiation exposure ($p=0.043$ for both parameters). Important factors that do not have an impact on the extent of resection are the tumour size, histological characteristics and cortex invasion.

Table 2: Analysis of factors influencing the extent of resection and its effect in the postoperative period [a]

Variable		GTR	STR	P-value
Female : Male		71 (65%): 38 (35%)	16 (52%): 15 (48%)	0.171
Age		56.08±13.31	56.14±14.53	0.802
Previous grade I meningioma (No: Yes)		98 (90%); 11 (10%)	25 (83%): 5 (17%)	0.338
Previous grade II meningioma (No: Yes)		100 (92%): 9 (8%)	27 (90%): 3 (10%)	0.722
Previous brain surgery (No : Yes)		89 (82%): 20 (18%)	20(%): 11 (%)	**0.043**
Previous radiation exposure (No : Yes)		104 (95%): 5(5%)	25(83%): 5 (17%)	**0.043**
Falx/Convexity/Tentorium : Skull base : Other		58 (53%): 43 (40%): 8 (7%)	15(48%): 7 (23%): 9 (29%)	**0.003**
Skull base (No: Yes)		66 (61%): 43 (39%)	24 (77%): 7 (23%)	0.084
Location exact	Convexity	**29 (97%)**	1 (3%)	**0.008**
	Sphenoid/ Sphenoorbital	**29 (85%)**	5 (15%)	
	Petroclival/clival	**6 (86%)**	1 (14%)	
	Falx	**9 (75%)**	3 (25%)	
	Multiple	**8 (75%)**	6 (25%)	
	Parasagital	**16 (66%)**	8 (33%)	
	Olfactory	**2 (66%)**	1 (33%)	
	Frontobasal	**3 (100 %)**	0 (0%)	
	Middle fossa floor	**2 (100%)**	0 (0%)	
	Cerebellum falx	**1 (100%)**	0 (0%)	
	Orbital	**1 (100%)**	0 (0%)	
	Tentorium	1 (33%)	**2 (66%)**	
	Intraventricular	1 (33%)	**2 (66%)**	
	Spinal	0 (0%)	**1 (100%)**	
	Falcotentorial	0 (0%)	**1 (100%)**	
Diameter (cm)		4.18±1.98	4.16±1.70	0.771
Oedema (No: Yes)		45 (43%): 59 (57%)	16 (59%): 11 (41%)	0.138
Oedema	No oedema	45 (74%)	16 (26%)	0.149
	Mild	39 (87%)	6 (13%)	
	Moderate	17 (85%)	3 (15%)	
	Severe	3 (60%)	2 (40%)	
	No info	5 (56%)	4 (44%)	
Bone invasion (No: Yes)		80 (74%): 28 (26%)	24 (77%): 7 (23%)	0.705
Arachnoid Invasion (No: Yes)		46 (43%): 62 (57%)	10 (32%): 21 (68%)	0.301
Sinus invasions (No: Yes)		99 (92%): 9 (8%)	15 (48%): 16 (52%)	**<0.0001**
Cortex invasion (No: Yes)		79 (73%): 29 (27%)	20 (65%): 11 (35%)	0.349
Histology: Atypical: Chordoid: Clear Cell		91 (83%): 16 (15%): 2 (2%)	27 (87%): 2 (6%): 2 (6%)	0.192
MIB		12.94±5.12	13.65±6.40	0.858
Mitotic index (<5 : ≥5)		19 (21%): 72 (79%)	1 (4%): 25 (96%)	0.043
Mitotic index (<8 : ≥8)		81 (89%): 10 (11%)	24 (92%): 2 (8%)	1.000
Surgical complications (No: Yes)		85 (78%): 24 (22%)	26 (84%): 5 (16%)	**0.475**
Hospital stay		15.34±14.47	16.13±7.89	**0.176**

[a] Data presented as mean (±standard deviation) or as number (percentage) of patients, where applicable. The p-values included in the table were obtained with Mann-Whitney tests for age (years), diameter (cm), MIB (%) and radiation dose (Gy). The remaining p values were obtained with chi-square tests or Fischer exact tests.

The analysis of the incidence of surgical complications following GTR revealed that the EOR is not associated with additional complications or a longer hospital stay (p=0.475 and 0.176 respectively). Nevertheless, more serious complications such as death, CNS ischaemia and CNS haemorrhage were exclusively found in this group (Figure 6).

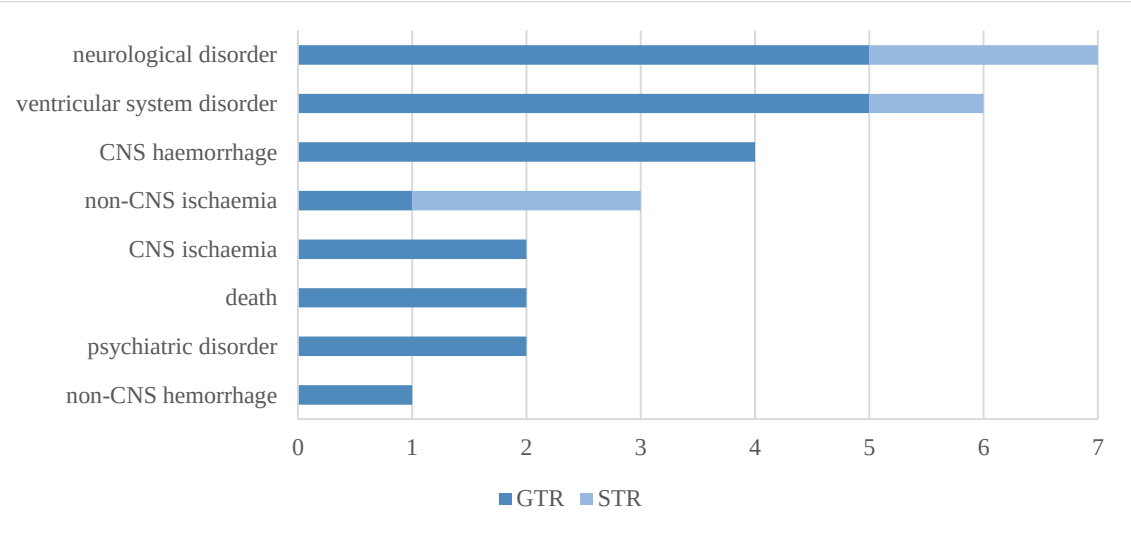

Figure 6 – Surgical complications according to the extent of resection (GTR and STR). [a]x axis: number of patients; y axis: complication types

Adjuvant Radiotherapy

Here we seek to assess which factors influenced the decision of recommending adjuvant radiotherapy after surgical resection. The ensuing analysis included age, gender, previous meningioma and irradiation history, tumour size, location, presence of oedema, adjacent structure invasion, histological characteristics and its resection outcome. Some differences can be observed between the patients undergoing adjuvant radiotherapy and those without it in terms of previous grade II meningioma, cortex and venous sinus invasion, Simpson's grades III and IV and a mitotic index ≥5, even though statistical significance was not attained (Figure 7 and Table 3).

Patients receiving adjuvant radiotherapy had both similar recurrence and multiple recurrence rates when compared to patients who did not receive this treatment. Of note, all patients who have progressed to grade III meningioma did not receive adjuvant radiotherapy, however this parameter did not reach statistical significance (Table 4).

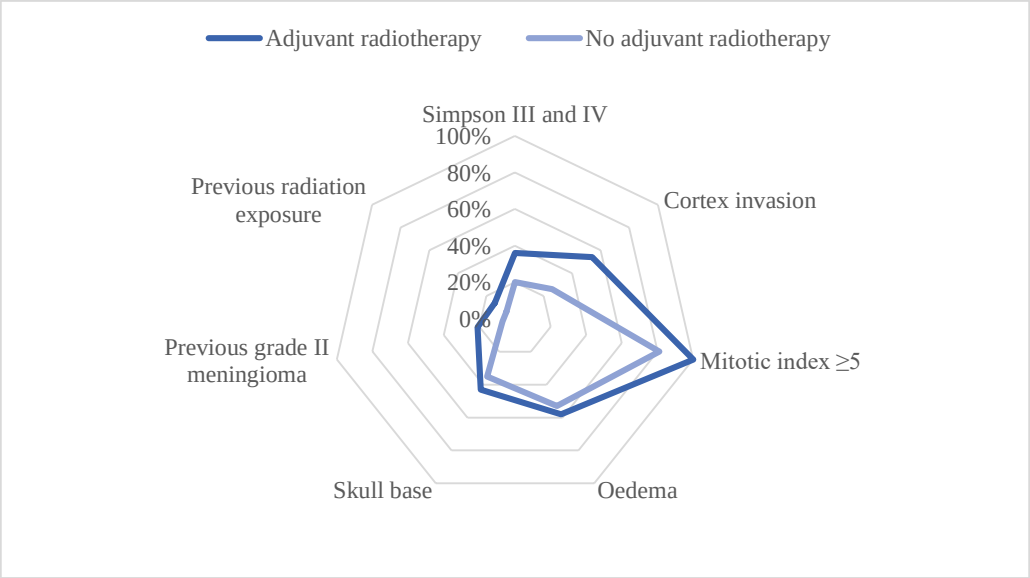

Figure 7 – Factors related with the recommendation of adjuvant radiotherapy

Table 3: Factors related with the recommendation of adjuvant radiotherapy [a]

Variable	Adjuvant radiotherapy	No adjuvant radiotherapy	P-value
Female: Male	9 (64%): 5 (36%)	78 (62%): 48 (38%)	0.862
Age	61.53±13.31	55.49±13.48	0.096
Previous grade II meningioma (No:Yes)	11 (79%): 3 (21%)	116 (93%): 9 (7%)	0.104
Previous radiation exposure	12 (86%): 2 (14%)	118 (94%): 8 (6%)	0.262
Diameter (cm)	3.99±1.60	4.20±1.95	0.850
Falx/Convexity/Tentorium : Skull base : Other	6 (43%): 6 (43%): 2 (14%)	67 (53%): 44 (35%): 15 (12%)	0.322
Skull base (No: Yes)	8 (57%): 6 (43%)	82 (65%): 44 (35%)	0.557
Oedema (No: Yes)	5 (42%): 7 (58%)	56 (47%): 63 (53%)	0.721
Histology - Atypical: Chordoid: Clear cell	14 (100%): 0 (0%): 0 (0%)	104 (83%): 18 (14%): 4 (3%)	0.245
Mitotic index (<5 : ≥5)	0 (0%): 14(100%)	20 (19%): 83 (81%)	0.124
Mitotic index (<8 : ≥8)	13 (93%): 1 (7%)	92 (89%): 11 (11%)	1.000
MIB	15.07±3.72	12.98±5.55	0.492
Bone invasion (No: Yes)	9 (69%):4 (31%)	95 (75%): 31 (25%)	0.738
Arachnoid Invasion (No: Yes)	4 (31%): 9 (69%)	52 (41%): 74 (59%)	0.561
Sinus invasions (No: Yes)	13 (100%): 0 (0%)	101 (80%): 25 (20%)	0.067
Cortex invasion (No: Yes)	6 (46%): 7 (54%)	93 (74%): 33 (26%)	0.052
GTR:STR	9 (64%): 5 (36%)	100 (80%): 26 (20%)	0.194

[a] Data presented as mean (±standard deviation) or as number (percentage) of patients, where applicable. The p-values included in the table were obtained with Mann-Whitney tests for age (years), diameter (cm) and MIB (%). The remaining p values were obtained with chi-square tests or Fischer exact tests.

Table 4: Adjuvant radiotherapy and meningioma recurrence / progression [a]

Variable	Adjuvant radiotherapy	No adjuvant radiotherapy	P-value
Recurrence (No: Yes)	10 (71%): 4 (29%)	74 (74%): 26 (26%)	1.000
Multiple recurrence (No: Yes)	13 (93%): 1 (7%)	90 (90%): 10 (10%)	1.000
Grade III progression	14 (100%): 0 (0%)	97 (97%): 3 (3%)	1.000

[a] Data presented as number (percentage) of patients, where applicable. The p-values were obtained with chi-square tests or Fischer exact tests.

Recurrence analysis

This analysis aimed to identify factors associated with higher recurrence rates. Therefore, parameters related to the patients' history, tumour and surgical procedure were considered. The most important were venous sinus and cortex invasion (p=0.018 and p=0.002), STR (p=0.009) and the grades of oedema (p=0.041). From the patients' history, older age (p=0.033), previous grade II meningioma (p=0.012) and previous brain surgery (p=0.014) were statistically significant. Previous radiation exposure (p=0.052) presented borderline results (Figure 8 and Table 5).

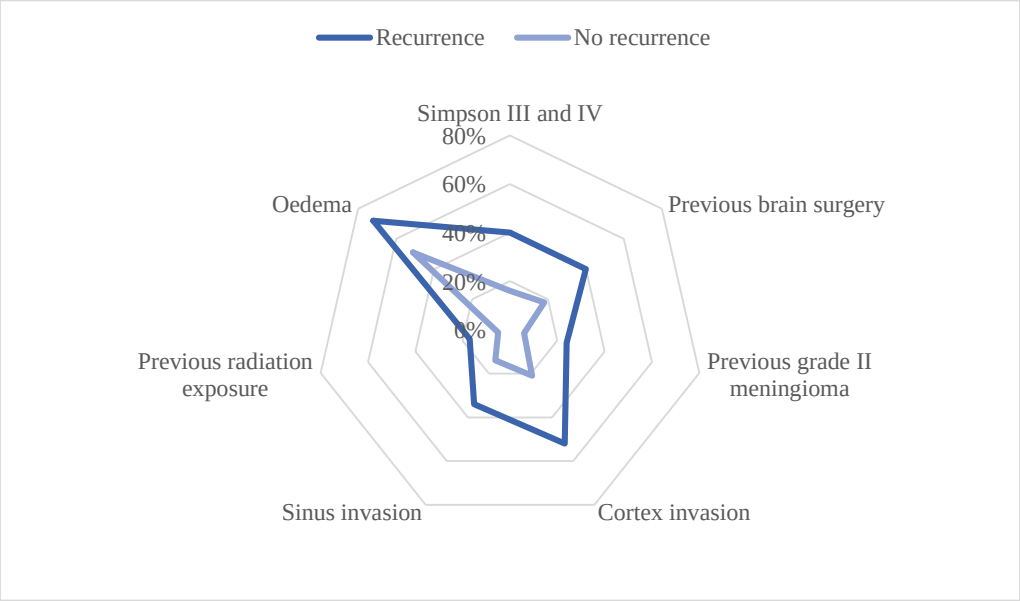

Figure 8: Risk factors distribution in recurrence group and no recurrence group

Table 5: Analysis of risk factors for recurrence [a]

Variable		Recurrence	No Recurrence	P-value
Female : Male		17 (57%): 13 (43%)	52 (62%): 32(38%)	0.614
Age		59.03±12.56	54.07±13.27	**0.033**
Previous grade I meningioma (No: Yes)		27 (93%); 2 (7%)	71 (85%): 13 (15%)	0.347
Previous grade II meningioma (No: Yes)		22 (76%): 7 (24%)	79 (94%): 5 (6%)	**0.012**
Previous brain surgery (No : Yes)		18 (60%): 12 (40%)	69 (82%): 15 (18%)	**0.014**
Previous radiation exposure (No : Yes)		25 (83%): 5 (17%)	80 (95%): 4 (5%)	0.052
Falx/Convexity/Tentorium : Skull base : Other		13 (43%): 10 (33%): 7 (23%)	43 (51%): 32 (38%): 9 (11%)	0.232
Skull base (No: Yes)		20 (66%): 10 (33%)	52 (62%): 32 (38%)	0.643
Diameter (cm)		4.83±2.24	4.03±1.75	0.116
Oedema (No: Yes)		7 (28%): 18 (72%)	40 (49%): 41 (51%)	0.060
Oedema	No oedema	7 (23%)	40 (48%)	**0.041**
	Mild	11 (37%)	28 (33%)	
	Moderate	6 (20%)	10 (12%)	
	Severe	1 (3%)	3 (4%)	
	No info	5 (17%)	3 (4%)	
Bone invasion (No: Yes)		21 (72%): 8 (28%)	60 (71%): 24 (29%)	0.919
Arachnoid Invasion (No: Yes)		10 (33%): 19 (66%)	35 (42%): 49 (58%)	0.496
Sinus invasions (No: Yes)		19 (66%): 10 (34%)	72 (86%): 12 (14%)	**0.018**
Cortex invasion (No: Yes)		14 (48%): 15 (52%)	66 (79%): 18 (21%)	**0.002**
Simpson	I	12 (40%)	45 (54%)	**0.050**
	II	6 (20%)	25 (30%)	
	III	7 (23%)	6 (7%)	
	IV	5 (17%)	8 (9%)	
GTR:STR		18 (60%): 12 (40%)	70 (83%): 14 (17%)	**0.009**
Histology: Atypical: Chordoid: Clear Cell		26 (87%): 3 (10%): 1 (3%)	71 (85%): 12 (14%): 1 (1%)	0.779
MIB		13.36±5.74	13.30±5.34	0.606
Mitotic index (<5 : ≥5)		5 (%): 21 (%)	10 (15%): 58 (85%)	0.753
Mitotic index (<8 : ≥8)		24 (92%): 2 (8%)	60 (88%): 8 (12%)	0.721
Adjuvant radiotherapy (No: Yes)		26 (87%): 4 (13%)	74 (88%): 10 (12%)	1.000
Radiation dose (Gy)		48.40±16.99	57.94±2.79	0.539
Surgical complications (No: Yes)		22 (73%): 8 (27%)	68 (81%): 16 (19%)	0.436

[a] Data presented as mean (±standard deviation) or as number (percentage) of patients, where applicable. The p-values included in the table were obtained with Mann-Whitney tests for age (years), diameter (cm), MIB (%) and radiation dose (Gy). The remaining p values were obtained with chi-square tests or Fischer exact test.

Survival analysis: extent of resection and adjuvant radiotherapy

The cohort mean progression free survival was 77.66±6.29 months (median: 81.00; 95% confidence interval 65.32-89.93) and the mean overall survival was 123.67±5.62 months (median: 138.00; 95% confidence interval: 112.66-134.68)/(Figure 9). The mean follow up was 46.12±37.87 months (median: 38.00; range 1 to 144 months).

Kaplan Maier analysis demonstrated an increased PFS in GTR compared to STR, with statistically significant log rank and Breslow tests (p=0.047 and p=0.033). The PFS for GTR at 1, 3 and 5 years was 92.0% (±3.1), 80.6% (±5.2) and 68.8% (±6.6) respectively, while for STR these values decreased to 84.0% (±7.3), 53.6% (±11.2) and 35.7% (±12.7) for the same time intervals. This association was not verified for the OS in which GTR and STR showed similar values (Figure 10 and Table 6).

In order to reduce potential bias, the analysis for the effect of adjuvant EBRT was divided according to the EOR. For GTR, this adjuvant treatment did not show any survival benefit. 5-year PFS and OS were 71.6% and 93.5% respectively for GTR alone and 32.8% and 65.6% for GTR with EBRT (Figure 11 and Table 7).

In STR, the opposite association was obtained, with patients who received adjuvant EBRT showing longer PFS and OS rates when compared to the STR alone group, even though this did not reach statistical significance. The 5-year PFS was 66.7% and 29.3% respectively for the STR with adjuvant EBRT group and for the STR only group. The OS was 100.0% and 84.7% for the same groups (Figure 12 and Table 8).

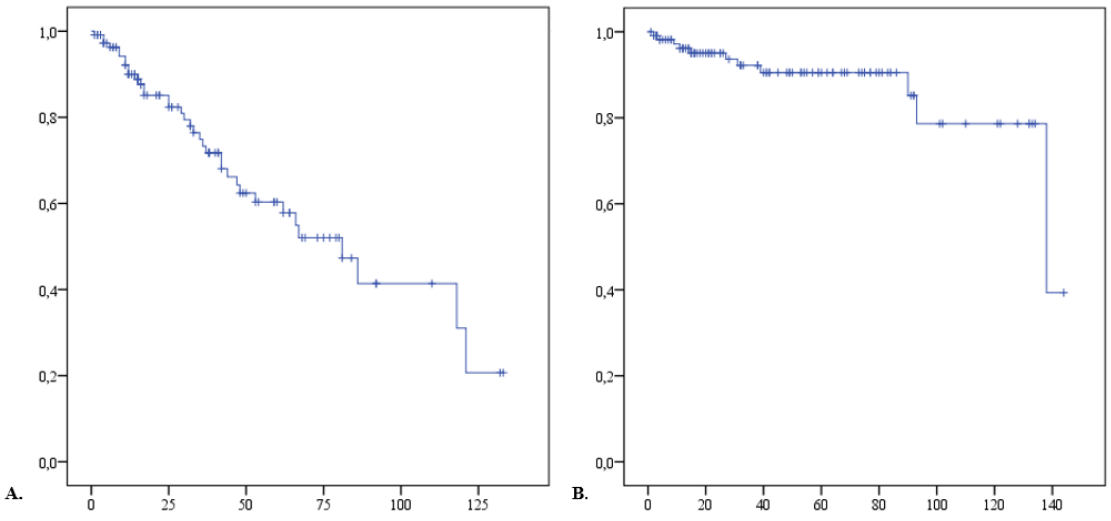

Figure 9 – Cohort progression free survival and overall survival. A: progression free survival, B: overall survival. x axis: time in months, y axis: proportion of patients.

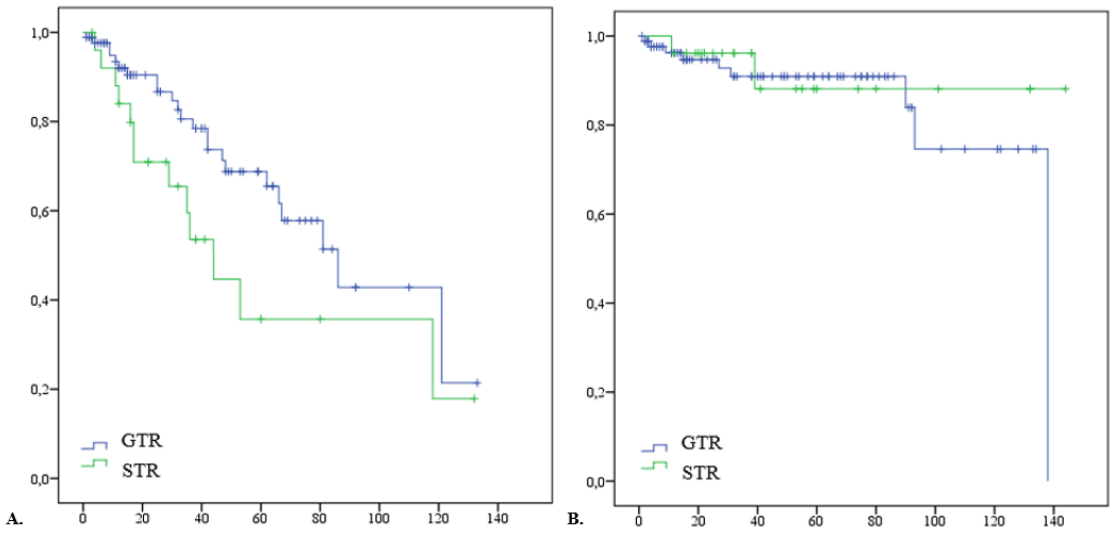

Figure 10 – Effect of extent of resection in PFS and OS. A: progression free survival, B: overall survival. x axis: time in months, y axis: proportion of patients.

Table 6: Effect of extent of resection in PFS and OS

Survival		***GTR (n=88)***	***STR (n=26)***
PFS	1 year	92.0% ±3.1	84.0% ±7.3
	3 year	80.6% ±5.2	53.6% ±11.2
	5 year	68.8% ±6.6	35.7% ±12.7
	Log-rank	0.047	
	Breslow	0.033	
OS	1 year	96.2% ±2.1	96.2% ±3.8
	3 year	90.9%±3.6	96.2% ±3.8
	5 year	90.9% ±3.6	88.1% ±8.4
	Log-rank	0.473	
	Breslow	0.775	

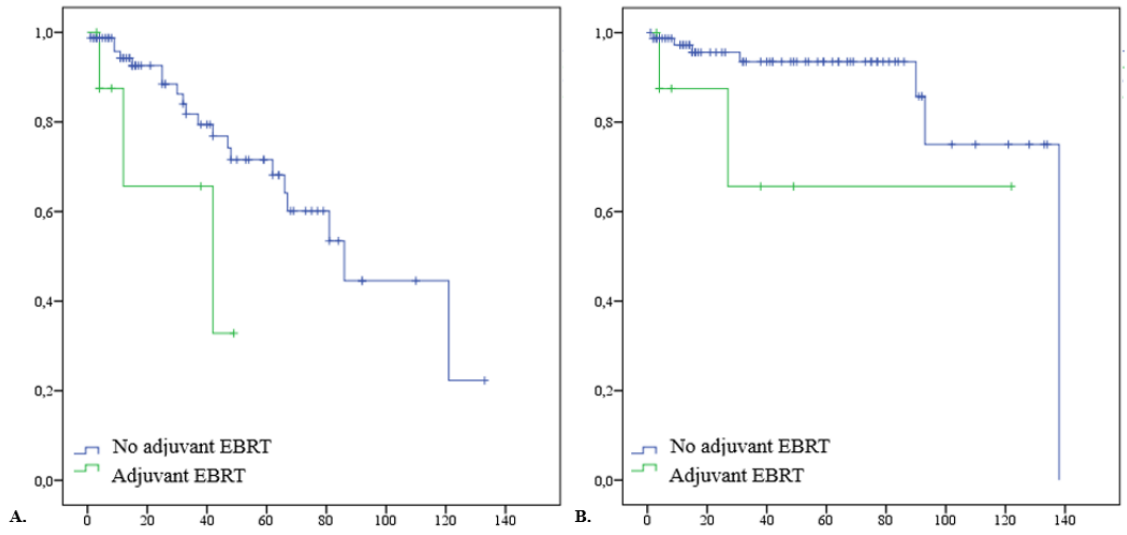

Figure 11: Effect of adjuvant EBRT in patients with GTR. A: progression free survival, B: overall survival. x axis: time in months, y axis: proportion of patients.

Table 7: Graph 5: Effect of adjuvant EBRT in patients with GTR

Survival		***Adjuvant EBRT (n=79)***	***No adjuvant EBRT (n=9)***
PFS	1 year	65.6% ±20.9	94.2% ±2.8
	3 year	65.6% ±20.9	81.8% ±5.4
	5 year	32.8% ±25.4	71.6% ±6.7
	Log-rank	0.059	
	Breslow	0.042	
OS	1 year	87.5% ±11.7	97.2% ±1.9
	3 year	65.6% ±20.9	93.5% ±3.2
	5 year	65.6% ±20.9	93.5% ±3.2
	Log-rank	0.081	
	Breslow	0.037	

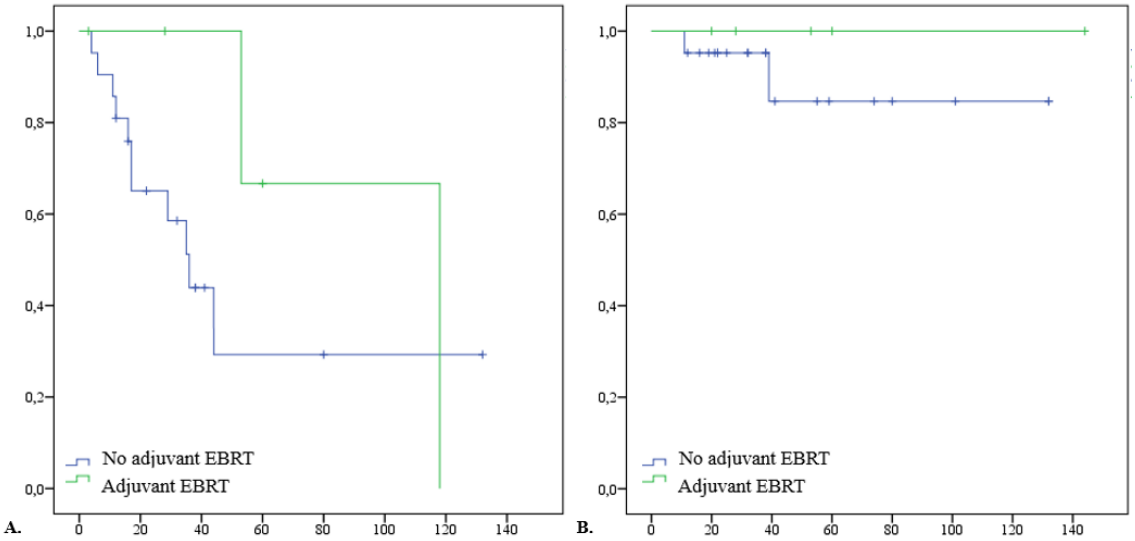

Figure 12: Effect of adjuvant EBRT in patients with STR. A: progression free survival, B: overall survival. x axis: time in months, y axis: proportion of patients.

Table 8: Effect of adjuvant EBRT in patients with STR

Survival		***Adjuvant EBRT (n=5)***	***No adjuvant EBRT (n=21)***
PFS	1 year	100.0%	81.0% ±8.6
	3 year	66.7% ±27.2	43.9% ±12.4
	5 year	66.7% ±27.2	29.3% ±12.5
	Log-rank	0.262	
	Breslow	0.122	
OS	1 year	100.0%	95.2% ±4.6
	3 year	100.0%	95.2% ±4.6
	5 year	100.0%	84.7% ±10.8
	Log-rank	0.450	
	Breslow	0.486	

V. Discussion

Summary of the study

This study analysed a cohort of 140 patients with histologically confirmed WHO grade II meningioma. Mean age at surgical intervention was 56 years and 62% of these patients were female. This data is congruent with the epidemiological description of such tumours although some series report a male gender predominance for non-benign meningiomas.[28] History of previous grade I and/or II meningiomas was present in 18.7% of the patients, previous brain surgery in 22.1% and history of radiation exposure in 7.1%. The fact that some patients (8.6%) had previous grade II meningioma allowed the differentiation of primary and recurrent grade II meningioma subgroups. This analysis revealed that recurrence patients had more history of previous irradiation ($p=0.005$) were less symptomatic ($p=0.033$) and had more adjacent structure invasion ($p=0.024$ for venous sinus and $p=0.012$ for cortex). They also registered increased recurrence rates ($p=0.012$) when compared with primary tumours.

For the primary surgical intervention, the vast majority of patients were symptomatic and presented with a wide range of symptoms, being the most frequent headache, visual impairment and seizures. This is corroborated by the variable tumour location, with the sphenoid or sphenoorbital, convexity and falx regions affected in more than half of the cases. Multiple meningiomas were present in 10% of the cases.

In 78% of the patients GTR was attained even though adjacent structure invasion was rather frequent. The analysis of factors limiting the EOR revealed that venous sinus invasion ($p<0.0001$) and tumour location ($p=0.003$) were the most important parameters. The mean tumour diameter was 4.18 ± 1.92 cm and this was not associated with decreased EOR. Mean hospital stay and complication rates were not affected by an aggressive operative strategy, with similar values reported in GTR and STR approaches. The overall intra-hospital mortality rate was 1.4%. The Kaplan Meier analysis reiterated the importance of complete resection in progression-free survival, with 5 year PFS of 68.8% for GTR and 35.7% for STR with a statistical significance for the log-rank and Breslow tests ($p=0.047$ and $p=0.033$).

Adjuvant therapy options at this stage were EBRT (for 14 patients) and chemotherapy with Imatinib (for 1 patient), with no associated complications. The recommendation of adjuvant EBRT improved both PFS and OS for the STR group without reaching statistical significance, most probably due to the reduced number of patients in this arm of the study.

In contrast, adjuvant radiotherapy did not show an improvement in PFS or OS in GTR patients. In fact, an inverse relation was seen with shorter PFS and OS in the group receiving adjuvant radiotherapy. Since the patients were not randomized, further analysis was performed in order to determine if there were additional factors contributing to this restriction. All GTR patients who received radiotherapy had meningiomas of the atypical histological subgroup and they did not show features of increased malignity such as higher MIB-1 or mitotic index. They also did not show any statistically significant differences regarding the patients' profile or tumour size or location. However, this group of patients had considerably more history of previous grade II meningioma (p=0.026) and also more cortex invasion (p=0.031) when compared to the non-irradiated GTR group. Also, there was an increase in post-surgical complications in this group, with approximately one half of the patients presenting some sort of complication (4 out of 9 patients: 2 with ventricular system disorders (hydrocephalus and CSF fistula), 1 with neurological disorder (motor aphasia) and 1 with intracranial abscess). These factors along with the group's small numbers might have contributed to this result. When the equivalent analysis was performed for the STR group, there were no such differences.

In general, more than one quarter of the patients had tumour recurrence during follow up (16.7% with one recurrence and 9.6% with multiple recurrence). At recurrence, 60% of the patients were asymptomatic and the mean tumour diameter was smaller comparatively to the previous episode (2.82±1.36 cm), most probably due to neuroradiological surveillance. Half of the cases resulted from local spread while the other half occurred due to CSF spread. In one third of the cases there were multiple locations. More complex treatment strategies were adopted for recurrent tumours and they included surgery, SRS, radiotherapy, chemotherapy, watchful waiting and combined treatment strategies. The overall recurrence risk factors were also studied and from these the most important were older age (p=0.033), previous grade II meningioma (p=0.012), previous brain surgery (p=0.014), sinus and cortex invasion (p=0.018 and p=0.002), STR (p=0.009) and higher grades of oedema (p=0.041).

The cohort mean progression free survival was 77.66±6.29 months (median: 81.00; 95% confidence interval 65.32-89.93) and the mean overall survival was 123.67±5.62 months (median: 138.00; 95% confidence interval: 112.66-134.68). The mean follow up was 46.12±37.87 months (median: 38.00; range 1 to 144 months). At the end of the follow up period 86.9% of the patients were stable, 3.5% were progressing and 9.6% were deceased,

with 3.5% of the deaths attributable to meningioma. Three patients (10% of the recurrent tumours) underwent malignant transformation to grade III meningioma.

Comparison with the existing literature

For this comparison, a Pubmed search of the English literature was performed combining the terms "atypical meningioma", "grade II meningioma" and "radiotherapy" (Table 9 and 10). This search only included studies with histological grading according to the WHO 2000 or 2007 classification system and if applicable with separate analysis of atypical and malignant meningiomas. These criteria were included because the previous classification system from 1993 was much less specific and also because in the present study grade III tumours were excluded to prevent bias from evaluating two types of tumours with a very different biological behaviour.

With reference to the extent of resection, the benefit of GTR in PFS and even in OS has been widely confirmed by several studies, regardless of the criteria used to define GTR (from Simpson grade I only to Simpson grade I-III) / (Tables 9 and 10). This factor seems to be the most important prognostic factor for survival.

The evidence obtained supports the idea that the role of adjuvant radiotherapy in atypical meningioma is still not fully understood. In fact, the great majority of the existing studies have not been able to demonstrate a statistically significant advantage in recommending adjuvant radiotherapy as part of the standard treatment, particularly for GTR. The meta-analysis from Hasan *et al*,[18] evaluating the role of radiotherapy following GTR included 14 studies with an overall number of 757 atypical meningioma patients. They have described a 5 year PFS of 62% for the GTR only group and 73% for the GTR and adjuvant radiotherapy group (p=0.057), as well as an OS of 85% and 88% for the same groups (p=0.95). Another meta-analysis from Fam and Eljamel[29], with 23 studies and 1575 patients, concluded that there was a benefit in adjuvant radiotherapy following GTR with a PFS of 73% for the GTR only group and 84% for the GTR and adjuvant radiotherapy group (p=0.036). Because of the timeline, both meta-analysis did not took into account one of the largest single centre studies from Sun *et al*,[10,30] which involved 151 GTR patients and established that there was no difference in PFS and OS in these groups of patients (p=0.83 and p>0.99). Despite the different outcomes, these two recent meta-analysis confirm that there is an enormous divergence between studies and that

prospective studies are required to elucidate this matter, expressly for adjuvant radiotherapy after GTR.

The evaluation of the effect of adjuvant radiotherapy following STR, appears to be less challenging and it presents more uniform results. Several studies have revealed that there is an advantage for PFS, however this does not seem to be the case for OS. For example, Park *et al* have reported a 5-year PFS of 0% for the STR only group (18 patients) and 68% for STR plus adjuvant radiotherapy group (7 patients)/($p<0.001$).[31] Sun *et al*, who have conducted one of the largest studies evaluating the role of adjuvant radiotherapy in STR also concluded that there was a benefit for these patients. The 5 year PFS was 30% for the STR only group (34 patients) and 65% for the STR and adjuvant radiotherapy group (25 patients)/($p=0.03$).[10] Despite this impact on PFS these studies could not show significant improvement in OS.

In general, several authors report only the p value for these groups and do not give information about the actuarial survival rates. This limits the comparison between studies, even though some have reached significant p values (e.g. Champeaux and Dunn[32]). In addition, other studies have assessed the effect of adjuvant radiotherapy on the overall cohort, without further division according to the extent of resection. These studies have reached inconsistent results with some reporting a substantial effect of adjuvant radiotherapy on PFS and others reporting no effect at all (e.g. Zaher *et al*[33] and Zhao *et al*[2]).

Table 9 – Effect of the extent of resection and adjuvant radiotherapy in the existing literature (part 1)

Authors	**No of cases (years)**	**GTR**	**GTR cases**	**Follow up GTR**	**Follow up STR**	**Benefit of GTR**	**ERBT after GTR**	**Follow up: GTR only**	**Follow up: GTR+ EBRT**	**Effect of ERBT**	**STR cases**	**EBRT after STR**	**Follow up: STR only**	**Follow up STR+ EBRT**	**Effect of ERBT**
Present study	114 (02/13)	I-II	88	69% 5 yrs PFS	36% 5 yrs PFS	**p=0.047 p=0.033**	9	72% 5 yrs PFS	33% 5 yrs PFS	p= 0.059	26	5	29% 5 yrs PFS	67% 5 yrs PFS	p= 0.262
Champeaux and Dunn, 2016[32]	178 (00/15)	I-III	142	-	-	**p=0.01**	24	-	-	**p< 0.001**	35	12	-	-	**p< 0.001**
Jenkinson *et al*, 2016[34]	133 (01/10)	I-III	113	81% 5 yrs PFS	40% 5 yrs PFS	**p=0.001**	32	82% 5 yrs PFS	80% 5 yrs PFS	p= 0.808	19	4	-	-	-
[b]Choy *et al*, 2016[35]	221 (NA)	I-II	172	-	-	**p<0.0001**	16	-	-	p= 0.633[c]	48	14	-	-	p= 0.633[c]
Cao *et al*, 2016[36]	41 (00/13)	I-II	28	56% 3 yrs PFS	29% 3 yrs PFS	**p=0.007**	Patients receiving RT: 21 PFS: p=0.427; OS: p=0.169[c]								
[a]Hasan *et al*, 2015[18]	757 (NA)	I-III	549	-	-	-	208	62% 5 yrs LC	73% 5 yrs LC	p= 0.057	-	-	-	-	-
Wang *et al*, 2015[16]	28 (01/09)	-	14	71% 3 yr FS	36% 3 yr PFS	**p=0.011**	3	87% 3 yrs PFS	100% 3 yrs PFS	p=0.18	14	9	0% 5 yrs PFS	49% 5 yrs PFS	p= 0.074
Zhao *et al*, 2015[2]	89 (01/11)	I-II	72	-	-	**p=0.021 (OS)**	Patients receiving RT: 40 PFS: p=0.442; OS: p=0.896[c]								
Aizer, *et al* 2015[37]	575 (04/09)	I-III	303	91% 5 yrs OS	78% 5 yrs OS	**p<0.001**	73	-	-	p= 0.320[c]	272	56	-	-	p= 0.320[c]
Nowak *et al*, 2015[38]	44 (00/09)	I-II	44	-	-	-	11	-	-	p= 0.079	-	-	-	-	-
[a]Fam and Eljamel, 2015[29]	1575 (NA)	-	297	-	-	-	86	73% 5 yrs PFS	84% 5 yrs PFS	***p*= 0.036**	80	63	47% 5 yrs PFS	47% 5 yrs PFS	*p*= 0.966

LC: local control, PFS: progression fee survival; OS: overall survival, reported p values apply for PFS unless stated otherwise; [a] Meta-analysis results; [b] Meta-analysis for chordoid meningiomas; [c] GTR and STR results combined.

Table 10 -Effect of the extent of resection and adjuvant radiotherapy in the existing literature (part 2)

Authors	No of cases	GTR	GTR cases	Follow up GTR	Follow up STR	Benefit of GTR	ERBT after GTR	Follow up: GTR only	Follow up: GTR+ EBRT	Effect of ERBT	STR cases	EBRT after STR	Follow up: STR only	Follow up STR+ EBRT	Effect of ERBT
Sun *et al*, 2014[10,30]	210 (93/12)	I-III	151	89% 5 yr PFS	48% 5 yr PFS	**p<0.001**	37	91% 5 yrs LC	100% 5 yrs LC	p=0.53	59	25	30% 5 yrs PFS	65% 5 yrs PFS	**p=0.03**
Hammouche *et al*, 2014[3]	79 (96/09)	I	34	74% 5 yrs PFS	32% 5 yrs PFS	**p=0.005**	9	68% 5 yrs PFS	100% 5 yrs PFS	p=0.13	45	27	-	-	None[§]
Choi *et al*, 2014[39]	72 (95/13)	I-II	53	92% 5 yrs OS	61% 5 yrs OS	**p<0.001[¥]**	42	-	-	p=0.28 (LC)	19	13	-	-	p= 0.070
Aboukais *et al*, 2013[40]	167 (94/11)	I-II	96	-	-	-	27[c]	-	-	**p= 0.039[c]**	71	27[c]	-	-	**p= 0.039[c]**
Hardesty *et al*, 2013[41]	258 (92/11)	I-II	149	85% 5 yrs PFS	54% 5 yrs PFS	**p<0.0001**	15	96% 5 yrs PFS	100% 5 yrs PFS	None[§]	79	20	60% 5 yrs PFS	80%5 yrs PFS	p=0.55
Park *et al*, 2013[31]	83 (97/11)	I-II	55	59% 5 yrs PFS	30% 5 yrs PFS	**p=0.002**	17	65% 5 yrs PFS	52% 5 yrs PFS	p=0.86	25	7	0% 5 yrs PFS	68% 5 yrs PFS	**p <0.001**
Lee *et al*, 2013[42]	90 (99/09)	I-III	71	85% 5 yrs PFS	70% 5 yrs PFS	**p=0.007**	17	65% 5 yrs PFS	74% 5 yrs PFS	p=1.00	19	17	20% 5 yrs PFS	91% 5 yrs PFS	**p= 0.002**
Zaher *et al*, 2013[33]	44 (09/12)	I-II	16	-	-	**p<0.0001**	Patients receiving RT: 26 **PFS: p=0.007[c]**								
Mair *et al*. 2011[43]	114 (01/10)	I-II	66	59% 5 yrs PFS	32% 5 yrs PFS	**p=0.018**	15	-	-	None[§]	48	15	14% 5 yrs PFS	43% 5 yrs PFS	**p=0.04**
Jo *et al*, 2010[44]	35 (97/08)	I	11	-	-	-	5	100% 3 yrs PFS	100% 3 yrs PFS	None§	23	16	34% 5 yrs PFS	63% 5 yrs PFS	**p= 0.011**

LC: local control, PFS: progression fee survival; OS: overall survival, reported p values apply for PFS unless stated otherwise; [c] GTR and STR results combined; [§] exact value was not reported; [¥]Atypical and malignant meningioma combined

Atypical Meningioma Management – Vienna's General Hospital Strategy

The attempt of recognizing the most common indications for recommending adjuvant radiotherapy in this centre could not find any statistically significant factors. Nevertheless, the tendency for this decision appeared to be based on factors such as previous grade II meningioma, cortex invasion and extent of resection (STR). These results reflect the lack of clear indications or protocols for this treatment option and the fact that this decision is the result of the healthcare team's best knowledge.

The first step of the management strategy is to achieve GTR and particularly Simpson grade I resections. Nevertheless, as mentioned before, this is not always possible due to anatomic limitations. If the tumour is accessible and can be removed in its vast majority, the localized remnants (e.g. adjacent to a venous sinus) can be managed with SRS, available in this centre as GammaKnife®. This option consists of a localised radiation therapy that damages tumour cells located in the irradiated area and spares the surrounding tissues. The target population for this technique are patients with small or residual tumours (maximum diameter of 3.5 cm) with a security distance of at least 3 mm from critical structures (e.g. the brainstem and the optic chiasm). In these cases the success rate of this treatment option is approximately 90%. Consequently patients can be managed as if GTR was accomplished and serial MRI should be performed during follow up in order to evaluate tumour recurrence.[45,46] On the other hand, STR patients who are not candidates for SRS should be seriously considered for adjuvant radiotherapy because of their increased risk for recurrence.

The MIB-1 parameter closely correlates with the tumour aggressiveness and in fact, studies indicate that atypical meningiomas with MIB-1 above 20% present mortality rates similar to malignant meningiomas.[8] For this reason, patients with high MIB-1 values (≥10%) or other histological characteristics of increased malignancy should also be considered for adjuvant radiotherapy even when GTR is achieved.

The same strategy should be applied to recurrent atypical meningioma, with the particularity that surgically untreatable recurrences or radio-resistant tumours are more likely to occur. In such cases, other treatment options should be considered, including chemotherapy, hormonal therapy, immunotherapy, therapy with radiopeptides, ion beam therapy or brachytherapy. Chemotherapy currently plays a minor role in the adjuvant treatment of meningiomas. Classic compounds, for instance hydroxyurea, have been included in this type of treatment, as well as new chemotherapy agents such as inhibitors of vascular endothelial growth factor receptor (VEGFR - Bevacizumab, Sutinib), platelet

derived growth factor receptor (PDGFR - Imatinib), epidermal growth factor receptor (EGFR - Erlotinib) and agonists of the somatostatin receptor (Sandostatin). Chemotherapy with Imatinib is the most commonly adopted scheme in this centre. The expression of sexual hormone receptors in some meningiomas advocates the use of antiprogesterone and antioestrogen agents such as Mifepristone and Tamoxifen, however their efficacy in atypical meningiomas is not certain. Immunotherapy with Interferon-alpha has shown promising results with the stabilization and remission of rapid growing and recurrent atypical meningiomas.[47,48] Radiopeptides targeting the somatostatin receptors are currently in phase II clinical trials and show potential as a treatment option for tumours with aggressive biological behaviour.[49] Ion beam radiotherapy is one of the most promising therapies for both atypical and anaplastic meningiomas. Proton and carbon ion therapies are thought to be the most valuable options and hopefully with the opening of the third European synchrotron research centre in Austria this treatment will become more available to atypical meningioma patients.[50] In cases of salvage therapy it is possible to consider brachytherapy. It consists in the implantation of radioactive "beads" containing iodine-125 in the tumour bed at the time of the operation. There is a very limited number of studies evaluating this treatment option, reporting small gains in OS with a noteworthy percentage of radiation necrosis.[51]

With this strategy in mind the following algorithm was developed (Figure 13).

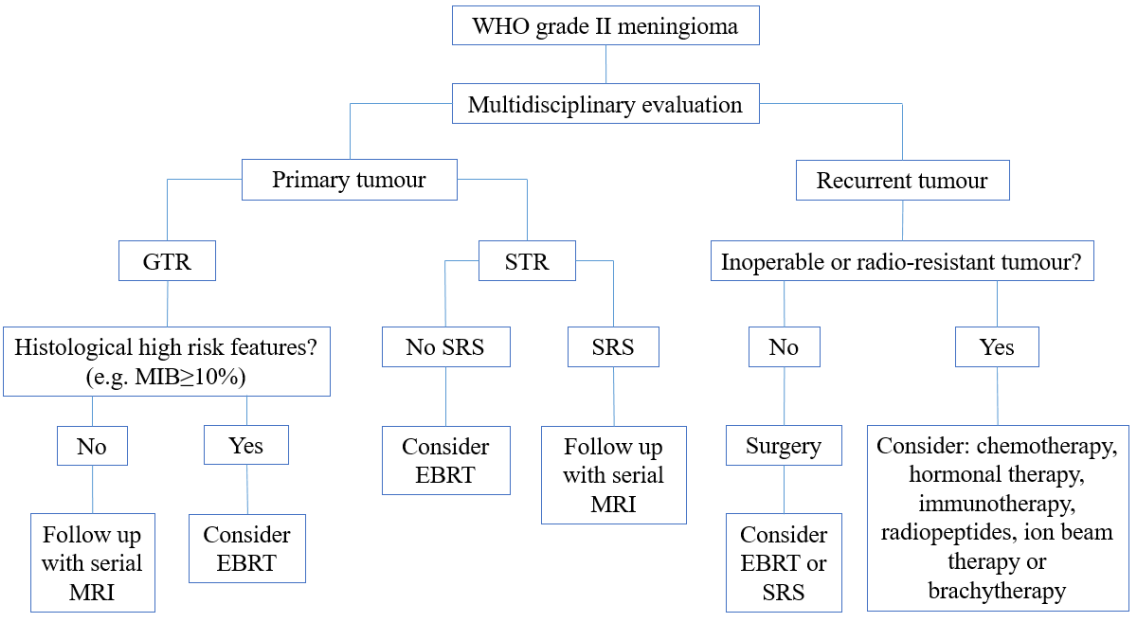

Figure 13 – Proposed algorithm for the management of atypical meningiomas

Limitations of the study

The most important limitations of this study are its retrospective nature and the fact that patients were not randomized for adjuvant radiotherapy. The irradiated group represented 10% of all patients and even though it was rather small it was consistent with the existing literature (range 7.4-59.1%).[32] These numbers are also supported by the work of Simon *et al* and Marcus *et al* who have conducted several surveys in Neurosurgery departments in Germany and the United Kingdom (UK).[52,53] They have concluded that the great majority of the centres would not recommend adjuvant radiotherapy following GTR surgeries (84% in Germany and 80% in the UK) and that only 26 to 41% of them would recommend it for STR patients.[1,52,53] Other important limitations of the study are the cohort heterogeneity (analysis of primary and secondary grade II meningiomas), the fact that Simpson grades were grouped into GTR and STR divisions in order to facilitate statistical analysis and also the relatively short follow up. In addition, due to the small number of recurrence patients receiving SRS and their diversity as a group, the effect of this treatment option was not further studied for this cohort. In reference to future studies, more histological characterization could provide important information about the variability of atypical meningiomas as a group. Despite these limitations, this is one of the largest single institution series considering WHO grade II meningiomas only.

Outlook

The upcoming "Radiotherapy versus Observation following surgical resection of Atypical Meningioma" (ROAM) trial from the European Organisation for Research and Treatment of Cancer (EORTC) will be the first prospective randomized study assessing the role of adjuvant radiotherapy in atypical meningioma. This will involve 190 patients in Europe and it aims to compare watchful waiting (with serial MRI) and EBRT (with 60 Gy in 30 fractions) as management options after GTR.[54] The results from this study are much expected as they may help to resolve one of the most discussed topics in Neurosurgery and shift the paradigm in the treatment of these patients.

VI. Conclusions

Although the registration of malignant tumours is mandatory in most countries, the same does not apply to benign or borderline tumours. For this reason, there is no long-term register for atypical meningioma and thus the exact incidence, prevalence, risk factor analysis and its natural history are not totally available at a global scale.[4] The aim of the present study was to provide a descriptive analysis of the cohort of grade II meningioma patients treated at the Vienna's General Hospital during the 12 year time period (2002-2013). In addition, the risk factors for recurrence, the role of the extent of resection and the effect of adjuvant radiotherapy were also evaluated.

Even though atypical meningiomas are not a malignant tumour they can assume a malignant course, with a much higher recurrence rate than WHO grade I meningiomas (8 fold higher).[1] Gross total resection is the gold standard treatment and it is associated with a longer PFS and consequently OS. Adjuvant EBRT is a reasonable option for STR patients, however this is still debatable for GTR patients in which watchful waiting might be as equally useful.

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Appendix

Table 1 – Patients' characteristics

Patients' characteristics	Number	%
Gender		
Male	53	37.9
Female	87	62.1
Age: Mean: 56.10±13.54; Median: 56.04; Min: 18.66; Max: 82.54		
Comorbidities		
Cardiovascular	62	44.3
Metabolic	49	35.0
Thrombotic	21	15.0
Oncologic	17	12.1
Psychiatric	17	12.1
Neurologic	15	10.7
Infectious	8	5.7
Autoimmune	4	2.9
Risk factors		
Previous brain surgery	31	22.1
Irradiation	10	7.1
Neurofibromatosis type 2	1	0.7
Previous meningiomas		
Previous grade 1 meningioma	16	11.4
Previous grade 2 meningioma	12	8.6
Previous grade 1 and 2 meningioma	2	1.4
Previous meningiomas of unknown histology	1	0.7

Table 2 – Patients' presentation symptoms

Presentation	Number	%
Symptomatic	124	88.6
Incidental	16	11.4
Presentation symptoms		
Headache	39	27.9
Visual impairment	29	20.7
Paresis	22	15.7
Seizure	22	15.7
Sensibility disorder	17	12.1
Personality disorder	17	12.1
Others*	14	10.0
Vertigo	10	7.1
Hearing disorder	10	7.1
Swelling	10	7.1
Aphasia	10	7.1
Ataxia	8	5.7
Disturbance of consciousness	8	5.7
Smelling disorders	7	5
Pain	6	4.3
Exophthalmos	2	1.4
Vesicolorectal disorder	2	1.4

*Others include nausea, vomiting, tremor, fine motor skills disorder, amnesia, asthenia and dysphagia

Table 3 – Tumours' characteristics: location, size, oedema and histological features

Tumours' characteristics	Number	%
Tumour location – exact		
Sphenoid/Sphenoorbital	34	24.5
Convexity	30	21.6
Parasagital	24	17.3
Multiple	14	10.1
Falx	12	8.6
Petroclival/clival	7	5
Olfactory	3	2.2
Frontobasal	3	2.2
Tentorium	3	2.2
Intraventricular	3	2.2
Middle fossa floor	2	1.4
Spinal	1	0.7
Falcotentorial	1	0.7
Cerebellum falx	1	0.7
Orbital	1	07
Tumour location – groups		
Falx/Convexity/Tentorium	73	52.1
Skull base	50	35.7
Intraventricular	3	2.1
Spinal	1	0.7
Multiple	13	9.3
Diameter (cm) Mean: 4.18±1.92; Median: 3.85; Min: 1.00; Max: 9.00		
Oedema		
No oedema	61	43.6
Mild	45	32.1
Moderate	20	14.3
Severe	5	3.6
Not available	9	6.4
Histology		
Atypic	118	84.3
Chordoid	18	12.9
Clear cell	4	2.9
Mitotic figures		
Mitotic index <5 : ≥5	20 : 97	17 : 83
Mitotic index <8 : ≥8	105 : 12	90 : 10
MIB (n=40 patients) Mean: 13.14±5.42; Median: 12.90; Min: 4.2; Max: 28.00		

Table 4 – Surgical outcome data: extent of resection, adjacent structure invasion, surgical complications, hospitalization length and adjuvant therapy

Surgical parameter	Number	%
Simpson		
I	72	51.4
II	37	26.4
III	17	12.1
IV	14	10
Invasion of adjacent structures		
Bone	35	25.0
Sinus	25	17.9
Arachnoid	83	59.3
Cortex	40	28.6
Complications (No: Yes)	111:29	79 : 21
Complications scale (Clavien Dindo)		
I. Minor pharmacological intervention	14	48.3
II. Major pharmacological intervention	6	20.7
III. Surgery, radio or endoscopic intervention	6	20.7
IV. Life threatening complication (Organ failure)	1	3.4
V. Death	2	6.9
Complication types		
Neurological disorder (e.g. hemiparesis, visual-field deficits, Jacksonian seizures)	7	24.1
Ventricular system disorder (e.g fistula and hydrocephalus)	6	20.7
CNS Haemorrhage	4	13.8
Ischaemic (non-CNS) (e.g. Pulmonary thromboembolism and deep vein thrombosis)	3	10.3
Ischaemic CNS	2	6.9
Psychiatric disorder	2	6.9
Infections	2	6.9
Haemorrhage (non-CNS)	1	3.5
Death	2	6.9
Hospital stay: Mean: 15,51±13.27; Median: 12,50; Min: 4; Max: 138		
Adjuvant treatment		
No adjuvant	125	89.3
Adjuvant radiation	14	10.0
Adjuvant chemo	1	0.7
Radiotherapy (Gy) Mean: 55,21±9.59; Median: 59,7 ; Min: 24.0 ; Max: 60.0		

Table 5 – Recurrence descriptive statistics

Recurrence	Number	%
Recurrence	30	26.3
Multiple recurrence	11	9.6
Symptoms		
Control scan	18	60.0
Multiple	4	13.3
Headache	2	6.7
Visual impairment	2	6.7
Exophthalmus	1	3.3
Seizure	1	3.3
Paresis	1	3.3
Aphasia	1	3.3
Location		
Multiple	10	33.3
Convexity	4	13.3
Sphenoid/sphenoorbital	4	13.3
Frontobasal	3	10
Parasagital	3	10
Falx	2	6.7
Olfactory	1	3.3
Tentorium	1	3.3
Petroclival/clival	1	3.3
Mid fossa floor	1	3.3
Spread type		
Local spread	16	53.3
CSF spread	14	46.7
Diameter (cm) Mean: 2.82±1.36; Median: 3.00 ; Min: 0.70; Max: 6.60		
Treatment		
GKN	10	33.3
Surgery and GKN	6	20.0
Surgery	4	13.3
Surgery and Radiation	3	10.0
Watchful waiting	3	10.0
Surgery, GKN and radiation	2	6.7
Radiation	1	3.3
Surgery, GKN; radiation and chemotherapy	1	3.3

Table 6– Follow up data: patients' status, grade III progression, PFS and OS

Status	Number	%
Stable	99	86.9
Meningioma related death	4	3.5
Progressing	4	3.5
Unknown cause of death	4	3.5
Non meningioma related death	3	2.6
Progression		
Progression to grade III	3	2.6
Progression free survival Mean: 35.82±31.01; Median: 27.00; Min: 1; Max: 133		
Overall survival Mean: 46.12±37.87; Median: 38.00; Min: 1; Max: 144		