BENEDITO JAMILSON ARAÚJO PEREIRA

Identificação de marcadores tumorais implicados na recorrência tumoral dos meningiomas atípicos

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo, para obtenção de título de Doutor em Ciências

Programa de Neurologia

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(Versão corrigida. Resolução CoPGr 6018/11, de 13 de outubro de 2011. A versão original está disponível na Biblioteca da FMUSP)

São Paulo
2021

Dados Internacionais de Catalogação na Publicação (CIP)

Preparada pela Biblioteca da
Faculdade de Medicina da Universidade de São Paulo

Pereira, Benedito Jamilson Araújo
Identificação de marcadores tumorais implicados na recorrência tumoral dos meningiomas atípicos / Benedito Jamilson Araújo Pereira. -- São Paulo, 2021.
Tese(doutorado)--Faculdade de Medicina da Universidade de São Paulo.
Programa de Neurologia.
Orientadora: Suely Kazue Nagahashi Marie.

Descritores: 1.Genes 2.Biomarcadores tumorais 3.Meningiomas atípicos 4.Preditor 5.Recidiva 6.Sobrevida

USP/FM/DBD-035/21

Responsável: Erinalva da Conceição Batista, CRB-8 6755

DEDICATÓRIA

Dedico esta tese de doutorado, aos meus pais Antônio Pereira da Silva e Maria Araújo Pereira, ao meu irmão Jailson Araújo Pereira, maiores incentivadores e responsáveis por todas as vitórias de minha vida.

A minha orientadora, Dra. Suely Kazue Nagahashi Marie, que acreditou no meu potencial, dedicando seu tempo para o desenvolvimento deste projeto, bem como para o meu desenvolvimento acadêmico.

Ao meu co-orientador, Dr Antônio Nogueira de Almeida, que além de participar ativamente de minha formação neurocirúrgica, me orientou quanto ao desenvolvimento acadêmico.

A toda equipe do laboratório LIM-15 do Hospital de Clínicas da Universidade de São Paulo, pelo seu empenho em me ajudar a desenvolver este projeto.

A minha companheira, Veruska Castanheira Frade, pela parceria e suporte durante toda essa jornada.

Aos meus professores Dr. Luciano Ferreira de Holanda e Dr. Rafael Rodrigues Holanda, por me orientarem nos primeiros passos da minha carreira profissional e por servirem de exemplo para minha vida.

Aos meus preceptores de residência Dr. Carlos Vanderlei Medeiros de Holanda, Dr. Jean Gonçalves de Oliveira e Dr. Ronie Leo Piske (in memorian) que desde o início de minha formação como neurocirurgião/ neurorradiologista intervencionista, me incentivaram e deram suporte ao desenvolvimento não só profissional, como também da parte acadêmica.

A todos os pacientes, que participaram desta tese, razão principal de nossa assistência e pesquisa.

AGRADECIMENTOS

Agradeço as pessoas que trabalham e compõem o laboratório LIM-15, especialmente nas figuras da Dra Suely Kazue Nagahashi Marie e da Dra Sueli Mieko Oba-shinjo, que me permitiram usufruir de todas as instalações, materiais, equipamentos além de suporte intelectual para o desenvolvimento da pesquisa.

Agradeço ao Dr. Antônio Nogueira de Almeida bem com a Sra. Ivoneide Estevão, na realização da busca ativa e reavaliação dos pacientes presentes neste estudo.

Agradeço ao departamento de neurocirurgia do hospital de clínicas da faculdade de medicina da universidade de São Paulo, por permitir estudar os casos atendidos.

Agradeço ao programa de pós-graduação em neurociências da Universidade de São Paulo (USP), ao corpo docente pelos conhecimentos adquiridos e pela oportunidade de realizar esta pós-graduação.

Agradeço ao colega, Dr. Ulysses Caus Batista, pelo companheirismo e apoio durante a realização da residência de neurorradiologia intervencionista, fundamentais para que eu iniciasse esse projeto.

Agradeço a pesquisadora Paula Sola, responsável pela preparação da biblioteca de alvos de exoma e experimentos em RNA-Seq.

Agradeço ao Dr. Antônio Marcondes Lerário, do departamento de medicina interna, divisão de metabolismo, endocrinologia e diabetes da University of Michigan, Ann Arbor, Michigan, USA, pelas análises estatísticas e de bioinformática, que contribuíram enormemente na análise dos resultados.

Agradeço a pesquisadora Alda Wakamatsu, do laboratório LIM14 do HCFMUSP, pelo preparo e análise da imuno-histoquímica. Agradeço a pesquisadora Aline Kawassaki Assato, do laboratório LIM 14 do HCFMUSP, pelo preparo dos materiais utilizando a técnica de tissue microarray (TMA).

Agradeço a convivência sempre profícua e harmoniosa com os meus colegas de pós-graduação atreladas ao laboratório LIM-15.

Agradeço ao laboratório de Sequenciamento em Larga Escala (SELA) da Rede PREMiUM da Faculdade de Medicina e do Hospital das Clínicas da FMUSP.

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RESUMO

Pereira BJA. *Identificação de marcadores tumorais implicados na recorrência tumoral dos meningiomas atípicos* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2021.

Introdução: Meningiomas são tumores que são originados das células meningoteliais e representam aproximadamente 30% de todos os diagnósticos neoplásicos do sistema nervoso central. O estudo sobre marcadores tumorais em meningiomas, que possam estimar prognóstico, tem crescido, porém ainda precisam de validação científica. Os meningiomas grau I são tumores benignos ou típicos, representando de 88–94% de todos os meningiomas. Os meningiomas atípicos são os de "grau intermediário" (grau II) que representam 4,7% – 7,2% dos meningiomas e estão associados a 29%–52% de recidiva após a ressecção. Adicionalmente, este grupo de tumores apresentam uma tendência à malignização, devido a maior propensão para migração da célula tumoral e infiltração do parênquima adjacente. A variante anaplásica (grau III) é mais rara, respondendo por 1% – 3% de todos os meningiomas, e são associados a um pobre prognóstico com média de sobrevida de 1,5 anos após o estabelecimento do diagnóstico. Objetivo: Identificar marcadores tumorais, que sejam preditores de recorrência em meningiomas atípicos (grau II da Organização Mundial da Saúde). **Materiais e Métodos**: Inicialmente, fizemos uma revisão da casuística do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP). Como segunda subsequente realizamos revisões bibliográficas, através da plataforma PubMed, para entender melhor a história natural da doença e suas particularidades, como: faixa etária, localizações tumorais específicas, tipo de apresentação clínica, resposta à radioterapia como tratamento adjuvante e características moleculares associadas aos meningiomas. Na última etapa do projeto realizamos estudo de exoma e transcriptoma por sequenciamento em larga escala em 91 casos com caracterização e seguimento clínicos de pelo menos 5 anos e em busca de marcadores moleculares preditivos de recorrência e progressão tumoral. **Resultados:** Na população jovem (abaixo de 20 anos), duas características se destacaram: predominância masculina e alta incidência de meningiomas atípicos; meningiomas localizados na região espinhal, predominaram na coluna torácica, sendo majoritariamente benignos; meningiomas localizados nos ventrículos cerebrais, são prevalentemente benignos, sendo

o subtipo fibroso o mais encontrado; meningiomas múltiplos, apresentaram predominância de tumores benignos, com a maioria dos tumores sendo pequenos e assintomáticos; tratamento adjuvante com a radioterapia, mostrou um impacto positivo na redução de recorrência, bem como prolongou o tempo livre de doença, embora resultados controversos também tenham sido observados na revisão da literatura. A abordagem molecular de larga escala do presente estudo revelou uma assinatura de expressão gênica relacionada ao ciclo celular e ao remodelamento da matriz extracelular como preditores de recorrência e progressão tumorais com impacto no tempo de sobrevida total e tempo de sobrevida livre de doença.

Conclusão: Os meningiomas atípicos apresentam uma reprogramação metabólica com ativação do metabolismo oxidativo, do ciclo celular, concomitantemente a um remodelamento da matriz extracelular que propicia a redução da adesão celular, perda do controle da migração celular e a evasão imune da célula tumoral. Foram identificados potenciais candidatos nestas vias de sinalização para novas estratégias terapêuticas para meningiomas atípicos.

Descritores: Genes; Biomarcadores tumorais; Meningiomas atípicos; Preditor; Recidiva; Sobrevida.

ABSTRACT

Pereira BJA. *Identification of tumor markers implied in the tumor recurrence of atypical meningiomas* [thesis]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2021.

Introduction: Meningiomas are tumors that originate from meningothelial cells and represent approximately 30% of all neoplastic diagnoses in the central nervous system. The studies on tumor markers in meningiomas, which can estimate prognosis, have grown, but still need scientific validation. Grade I meningiomas are benign or typical tumors, accounting for 88–94% of all meningiomas. Atypical meningiomas are "intermediate grade" (grade II) which represent 4.7% - 7.2% of meningiomas and are associated with 29% –52% of recurrence after resection. Additionally, this group of tumors has a tendency towards malignancy, due to a greater propensity for cell migration and infiltration of the adjacent parenchyma. The anaplastic variant (grade III) is rare, accounting for 1% - 3% of all meningiomas, and is associated with a poor prognosis with a mean survival of 1.5 years after establishing the diagnosis. **Objective**: To identify tumor markers that are predictive of recurrence in atypical meningiomas (WHO grade II). **Methods**: Initially, we reviewed the casuistry of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP). As subsequent stage, we carried out bibliographic reviews, through the PubMed platform, to better understand the natural history of the disease and its particularities, such as: age group, specific tumor locations, type of clinical presentation, response to radiotherapy as an adjuvant treatment and molecular characteristics associated with meningiomas. In the last stage, we performed an exome and transcriptomic analysis of 91 selected cases with clinical characterization and follow-up for at least 5 years to search for predictive molecular markers of tumor recurrence and tumor progression. **Results**: In the young population (under 20 years old), two characteristics stood out: male predominance and high incidence of atypical meningiomas; meningiomas located in the spinal region predominated in the thoracic spine, being mostly benign; meningiomas located in the cerebral ventricles were predominantly benign, being the fibrous subtype the most found; multiple meningiomas presented as benign tumors, being the majority of tumors small and asymptomatic; adjuvant treatment with radiotherapy showed a positive impact in

reducing recurrence, as well as prolonging disease-free time, although controversial results were also observed in the literature review. The high throughput sequencing approach of the present study revealed a gene expression profile related to cell cycle and extracellular matrix remodeling as predictive markers of tumor recurrence and tumor progression with impact in overall survival time and disease-free survival time. **Conclusion:** The atypic meningiomas presented a metabolic reprogramming with activation of oxidative metabolism, concomitant to an extracellular matrix remodeling, which provided cell-adhesion decrease, loss of cell migration control and immune evasion of the tumoral cell. Potential candidates for new therapeutic strategies for atypical meningiomas were identified in these signaling pathways.

Descriptors: Genes; Biomarkers, tumor; Atypical meningioma; Predictor; Recurrence; Survival.

INTRODUÇÃO

Meningiomas são tumores que são originados das células meningoteliais e representam aproximadamente 30% de todos os diagnósticos neoplásicos do sistema nervoso central (2). De acordo com a classificação de 2016 da Organização Mundial de Saúde (OMS) (3), eles são classificados em três graus. Os meningiomas grau I são tumores benignos ou típicos, estratificados em nove subtipos histológicos: meningotelial, fibroso, transicional, psamomatoso, angiomatoso, microcístico, secretório, linfo-plasmocítico e metaplásico representando de 88–94% de todos os meningiomas (4). Os meningiomas atípicos são os de "grau intermediário" (grau II) que representam 4,7% – 7,2% dos meningiomas e estão associados com 29%–52% de recidiva após a ressecção (5). Adicionalmente, este grupo de tumores apresentam uma tendência à malignização, devido a maior propensão para migração celular e infiltração do parênquima adjacente (6). A variante anaplásica (grau III) é mais rara, respondendo por 1% – 3% de todos os meningiomas (7) e são associados a um pobre prognóstico com média de sobrevida de 1,5 anos após o estabelecimento do diagnóstico (8).

O diagnóstico de meningioma e seu tratamento impactam importantemente nas atividades diárias dos pacientes (9). Pacientes com meningioma podem apresentar déficits clínicos antes da cirurgia, mas o procedimento cirúrgico de ressecção do tumor pode agravar os déficits já existentes, mas podem também acrescentar outros déficits específicos, como comprometimento da visão em pacientes com tumor localizado próximo ao nervo óptico ou afasia em pacientes com tumor na convexidade próximo à área de Brocca (10). Em pacientes com meningiomas GI, a ressecção cirúrgica completa, apesar de ser um objetivo a ser alcançado, deve ser vista com parcimônia, visto que o procedimento em si pode acarretar co-morbidades e/ou complicações que implicarão no desfecho da doença (11). No entanto, em pacientes com meningiomas GII ou GIII, a ressecção total do tumor mostrou ser a melhor chance para aumento de sobrevida e tempo livre da doença (12). Tratamentos adjuvantes como a radioterapia (RT), mostraram um impacto positivo na redução de recorrência, bem como no prolongamento do tempo livre de doença (1).

O estudo dos meningiomas, assim como de outros tumores, está passando por uma nova fase devido às pesquisas cada vez mais robustas nos campos de investigação de perfis moleculares, genômicos e epigenéticos. Essas abordagens sistemáticas, em larga escala, têm adicionado uma taxonomia molecular, que têm estratificado o

diagnóstico segundo uma classificação molecular da doença e determinado um manejo clínico específico com desfechos clínicos mais favoráveis. Esta análise combinada têm permitido uma compreensão mais abrangente dos mecanismos de progressão tumoral e, consequentemente, uma abordagem clínica mais personalizada para os pacientes (13). Até o momento, nenhum consenso foi estabelecido sobre biomarcadores específicos para diagnóstico precoce ou prognóstico de pacientes com meningiomas, sobretudo marcadores de recorrência tumoral. Considerando-se que cerca de 20% dos meningiomas não apresentam mutação somática (14) e a evolução é fatal nos pacientes com meningiomas GII recorrentes, a proposta do presente estudo foi identificar marcadores tumorais preditores de recorrências de meningiomas atípicos passíveis de serem aplicados para a melhora do desfecho clínico destes pacientes.

OBJETIVOS

Objetivo Geral

Identificar marcadores tumorais, que sejam preditores de recorrência em meningiomas atípicos (grau II da OMS).

Objetivos Específicos

- Sistematizar as características da casuística do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP) através de preenchimento de protocolo clínico uniformizado e recuperação dos detalhes do seguimento clínico através de chamadas telefônicas e telegramas ("*recall*"). Analisar os dados clínicos organizados e traçar paralelos com os disponíveis na literatura médica, com ênfase nos impactos da cirurgia e do tratamento adjuvante na evolução clínica dos pacientes. Analisar o estado clínico no momento da recorrência do tumor, o tratamento adjuvante aplicado, a evolução clínica e eventualmente as causas da morte;

- Analisar se os subtipos histológicos de meningioma, faixa etária, sítios tumorais e/ou apresentação clínica com multiplicidade tumoral ou sangramento apresentam correlação com sobrevida e recorrência;

- Avaliar o impacto da radioterapia, na nossa coorte e em dados publicados na literatura, na taxa de recorrência dos meningiomas atípicos;

- Sistematizar os achados moleculares descritos previamente na literatura relacionados aos mecanismos moleculares implicados na tumorigênese;

- Analisar o perfil exômico e transcriptômico dos meningiomas, comparando meningiomas grau I e grau II, à procura de alvos preditores de progressão tumoral e de recorrência, com potencial para aplicabilidade no manejo clínico destes pacientes.

METODOLOGIA

Amostras Tumorais

Amostras tumorais provenientes de cirurgias de ressecção de meningiomas foram coletados pelo grupo de neurocirurgia do Departamento de Neurologia do HC-FMUSP.

Os tecidos foram congelados imediatamente após ressecção cirúrgica e mantidos em nitrogênio líquido até análise pela esquipe do laboratório LIM-15 durante a execução do projeto Genoma Clínico e Projeto Temático sobre Tumores do Sistema Nervoso Central (projetos FAPESP #01/12898-4 e 04/12133-6). Todos os pacientes assinaram consentimento informado para a doação do material biológico remanescente após a sua utilização para o estabelecimento do diagnóstico histopatológico para formação do biorepositório. Todas as amostras que foram utilizadas no presente estudo fazem parte do biorepositório construído durante o desenvolvimento dos dois projetos mencionados acima, com a aprovação da Comissão de Ética para análise de Projetos de Pesquisa da Diretoria Clínica do HC-FMUSP (CAPPesq # 691/05) e aprovação da CONEP (3317, parecer 373/2002).

Desenho do estudo

Inicialmente, fizemos uma revisão da casuística do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP). Os pacientes com diagnóstico de meningioma submetidos à cirurgia entre 2000 e 2014 foram incluídos no presente estudo. Pacientes menores de 18 anos, pacientes com lesões na medula espinhal e aqueles com menos de 12 meses de acompanhamento foram excluídos do estudo.

A segunda etapa do nosso projeto, foi realizar revisões bibliográficas, baseados em trabalhos publicados na literatura, com acesso através da plataforma PubMed, para entender melhor a história natural da doença e suas particularidades, como: faixa etária (populações pediátrica e adulta); localizações tumorais específicas como ventriculares e espinhais; tipo de apresentação (tumores múltiplos e tumores hemorrágicos); radioterapia como tratamento adjuvante e características moleculares associadas aos meningiomas.

Após as meta-análises, um grupo de 91 pacientes com meningioma intracraniano diagnosticados na HC-FMUSP entre junho de 2000 e novembro de 2007 foram selecionados para o estudo de identificação de marcadores preditores de recorrência de

meningiomas atípicos, Os critérios de inclusão foram: 1) meningioma recém-diagnosticado após ressecção primária, confirmado por histopatologia; 2) amostra de tumor congelada disponível no biorepositório de tumor cerebral do LIM-15; 3) ressecção maior que 80% do volume tumoral e 4) pelo menos 60 meses de acompanhamento. Os critérios de exclusão incluíram: 1) história prévia de tratamento, seja cirurgia ou irradiação cerebral e 2) idade menor que 18 anos. Os casos foram estratificados de acordo com a classificação da OMS de 2016(15), por neuropatologistas experientes em preparação de parafina. Os fragmentos de tumor coletados foram macrodissecados para excluir áreas hemorrágicas e foram imediatamente congelados em nitrogênio líquido. As amostras congeladas foram criosseccionadas com espessura de 4 mm, coradas com hematoxilina-eosina e analisadas em microscópio de luz. Necrose, restos celulares e áreas não neoplásicas foram microdissecados antes da extração do RNA, conforme relatado anteriormente (16, 17). A sobrevivência livre de progressão radiográfica tumoral (PFS) foi medida a partir da data da cirurgia primária até a primeira data de recorrência tumoral radiográfica documentada após ressecção macroscópica total (GTR) ou crescimento de doença residual após ressecção subtotal.

O consentimento informado para o uso do tecido foi obtido de cada paciente no momento da cirurgia, de acordo com as diretrizes éticas aprovadas pela Faculdade de Medicina da Universidade de São Paulo (protocolo de pesquisa 200/05-63079616.2.0000.0065). Os prontuários médicos foram consultados para a obtenção das informações demográficas, características do tumor, detalhes do tratamento, progressão do tumor e óbito, que foram registrados no protocolo de pesquisa. Os dados de seguimento dos pacientes sem seguimento ambulatorial ativo foram completados através das informações obtidas na chamada telefônica.

As metodologias utilizadas em cada um dos desenhos experimentais, assim como as análises estatísticas aplicadas estão descritas detalhadamente em cada publicação apresentadas a seguir.

RESULTADOS

Caracterização demográfica e clínica da casuística analisada

Um total de 629 pacientes com diagnóstico de meningioma foram submetidos ao tratamento cirúrgico entre 2000 e 2014. Pacientes menores de 18 anos e pacientes com meningioma na medula espinhal não foram incluídos no presente estudo. Assim como 36 casos com seguimento clínico abaixo de 12 meses foram excluídos. Dessa forma, a série de meningiomas analisada constituiu-se de 593 pacientes (442 mulheres e 151 homens; 2,9 mulheres para cada homem), com 52,8 ± 13,8 anos de idade na época da cirurgia e com seguimento médio de 68,8 ± 48,9 meses. Os dados de neuroimagem quanto as localizações do tumor foram analisadas de 434 pacientes e os subtipos histopatológicos foram revistos em 395 casos. Os dados clínicos incluindo escala de performance de Karnofsky (KPS), estado neurológico, medicamentos em uso e informações sobre óbito fora do hospital foram obtidos de 379 pacientes por meio de atendimento ou entrevistas por telefone. Os entrevistados também foram questionados se os pacientes melhoraram, permaneceram estáveis ou pioraram após a cirurgia.

Mortalidade: No total, foram identificados 104 óbitos na série (86 com GI, 14 com GII e 4 com GIII), sendo que 6 deles ocorreram com mais de dez anos de seguimento. Sessenta e oito mortes foram relacionadas à cirurgia ou recorrência / progressão do tumor (morte relacionada ao tumor) e 36 de outras causas, como eventos cerebrovasculares, outros tumores e distúrbios clínicos como insuficiência pulmonar ou hepática. Algumas famílias não souberam informar a causa do óbito não relacionado ao tumor, sendo esses casos classificados como indefinidos.

O grau histológico foi o fator com maior impacto na sobrevivência. A sobrevida de dez anos foi observada em 85% do GI, 35% do GII e 0% do GIII. Os testes log-rank comparando as curvas de sobrevivência entre GI e GII (valor p <0,0001) e GII e GIII (valor p = 0,0001) foram altamente significativos. Nenhum paciente com GIII sobreviveu mais do que 25 meses após o diagnóstico.

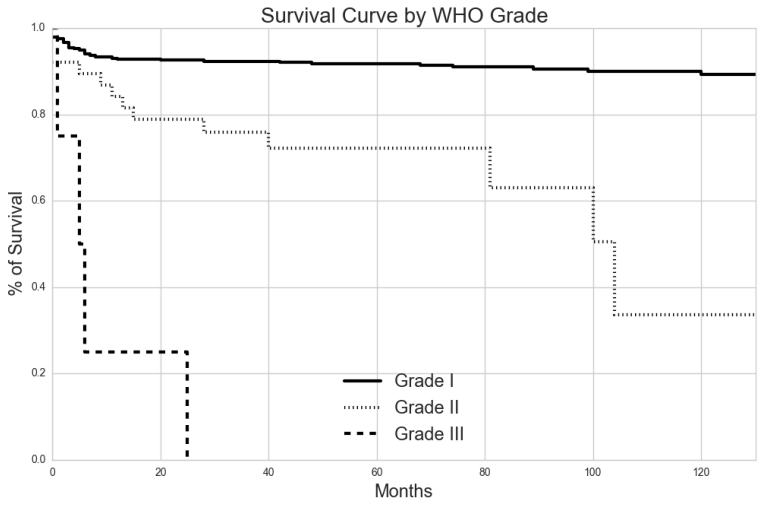

Figura 1: Curvas de sobrevivência agrupadas por grau histológico.

O padrão de mortalidade ao longo do tempo mudou de acordo com a causa da morte. Após dois anos de cirurgia, as mortes não relacionadas ao tumor foram sete vezes mais frequentes do que as mortes relacionadas ao tumor (odds ratio 7,1; IC 95% 2,8 a 19,5; p <0,0001). No GI, 76,5% dos óbitos relacionados ao tumor ocorreram até um ano após a cirurgia, enquanto 85,7% dos óbitos não relacionados ao tumor ocorreram após esse período. No GII e GIII, 47% dos óbitos relacionados ao tumor ocorreram no primeiro ano de pós-operatório, e apenas um paciente faleceu por causas não relacionadas ao tumor.

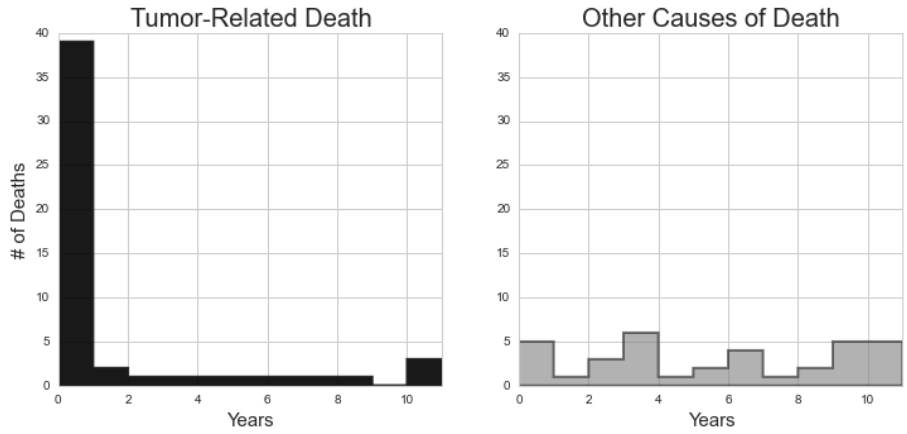

Figura 2: Padrão de distribuição dos óbitos ao longo dos anos de acordo com a causa do óbito.

Recorrência: Neste trabalho, o intervalo livre de recorrência foi considerado o tempo entre a primeira cirurgia e o primeiro tratamento subsequente (seja radioterapia ou novo

procedimento cirúrgico). Esse conceito foi usado para evitar a diferenciação subjetiva de restos de tumor de cicatrizes próximas aos locais de ressecção. 42 de 551 (25,8%) pacientes com GI e 24 de 42 (57,1%) com GII / GIII foram submetidos a tratamento complementar após a cirurgia. Em 10 pacientes, a segunda terapia foi outra intervenção cirúrgica, em 125 pacientes foi radioterapia e em 31 cirurgia e radioterapia combinadas. A recorrência do tumor não refletiu no aumento da incidência de mortalidade em pacientes com meningiomas GI. Além disso, a necessidade de tratamento adicional não prejudicou significativamente a capacidade de realizar atividades diárias independentes para a maioria dos pacientes GI (odds ratio 1,7; IC 95% 0,7 a 4,2; p = 0,242). No entanto, todos os pacientes com GII ou GIII que recidivaram morreram.

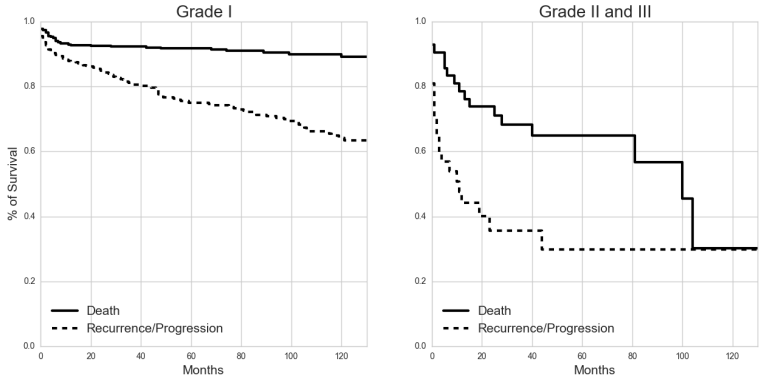

Figura 3: Relação entre recorrência tumoral e óbito em diferentes graus histológicos.

Localização do tumor: o sítio de ressecção afetou a incidência de recorrência, mas não a taxa de sobrevivência. Os tumores de convexidade tiveram cerca de metade do risco de recorrência em comparação com todas as outras localizações juntas (odds ratio 0,4; IC 95% 0,27 a 0,67; p = 0,0002). Pacientes com tumores na área supratentorial (odds ratio 1,7; 95% CI 1,0 a 2,7; p <0,05) e na área falcotentorial (odds ratio 2,1; IC 95% 1,3 a 3,5; p <0,005) apresentaram cerca de duas vezes mais de chance de recorrência em comparação com pacientes com tumores na convexidade. A recorrência na área petroclival também foi maior do que na convexidade, mas não foi significativa (odds ratio 1,5; IC 95% 0,8 a 2,9; p = 0,2859). Cada variável foi analisada pelo método de teste de regressão simples que demonstrou que: 1) os tumores localizados na região ventricular eram de maior grau de malignidade (IC = 2,2031 a 46,8823; p = 0,003), enquanto os tumores localizados na base o crânio eram de menor grau de malignidade (IC = 0,2008 a

0,8212; p = 0,0121); 2) o subtipo meningotelial localizou-se mais frequentemente na base do crânio (IC = 1,1612 a 2,6364; p = 0,0075); 3) não houve relação entre o grau de malignidade do tumor e a localização do tumor na convexidade (IC = 0,8795 a 3,1876; p = 0,1166) e 4) sexo masculino foi associado a maior risco de malignidade (IC = 1,0256 a 3,5745; p = 0,0414). Nenhuma associação com o gênero e o local do tumor foi encontrada (gênero vs. base do crânio: CI = 0,4705 a 1,1947; p = 0,2257; gênero vs. convexidade: CI = 0,7467 a 1,8650; p = 0,4783; ou gênero vs. região ventricular: CI = 0,8336 a 17,2204; p = 0,0846).

Tabela 1: Locais do tumor e seus subtipos histológicos.

		convexidade		Base de crânio		ventricular		total	
		n	%	N	%	n	%	n	%
GRAU I		199	50.37	144	36.45	3	0.75	346	87.6
Subtipo histológico	meningotelial	88	22.27	78	19.74			166	41.91
	transicional	77	19.49	51	12.91	1	0.25	129	32.65
	fibroso	25	6.32	13	3.29	2	0.5	40	10.12
	microcístico	5	1.26					5	1.26
	angiomatoso	3	0.75	1	0.25			4	1.01
	psamomatoso			1	0.25			1	0.25
	secretor	1	0.25					1	0.25
GRAU II		28	7.08	9	2.27	3	0.75	40	10.1
GRAU III		6	1.51	2	0.5	1	0.25	9	2.3
TOTAL		233	58.98	155	39.24	7	1.77	395	100

De 379 famílias entrevistadas, 325 pacientes estavam vivos. Dos sobreviventes, 109 estavam em terapia anticonvulsivante (13 com convulsões frequentes), 4 tinham déficits motores, 20 tinham algum grau de perda visual (de tumores removidos próximo ao nervo óptico) e 9 desenvolveram afasia. Apesar dos déficits, quando questionados sobre o impacto da cirurgia em suas vidas, 96,3% relataram que os pacientes melhoraram ou mantiveram o mesmo estado neurológico após o procedimento.

Tabela 2: Relação entre local do tumor e sexo com malignidade

Variável	sim	não	95% Intervalo de confiança	Odds Ratio	p Value
VENTRICULAR					
Grau I	3	343	2,2031 - 46,8823	10,163	0,003
Grau II/III	4	45			
CONVEXIDADE					
Grau I	199	147	0,3137 - 1,1370	0,5972	0,1166
Grau II/III	34	15			
BASE DE CRÂNIO					
Grade I	144	202	1,2177 - 4,9805	24,626	0,0121
Grau II/III	11	38			
Meningotelial	78	88	1,1612 - 2,6364	17,497	0,0075
Outros subtipos	77	152			
GRAU II/III					
Masculino	19	86	1,0256 - 3,5745	19,147	0,0414
Feminino	30	260			

Análise Crítica

Nossa casuística de meningiomas (18) confirmou que pacientes com este tipo de tumor apresentam um bom prognóstico a longo prazo, com uma taxa de sobrevida global em torno de 80% em dez anos, corroborando os dados prévios da literatura (19). Cerca de 96% dos pacientes relataram melhora ou inalteração do estado clínico após o tratamento cirúrgico. No entanto, a presente análise mostrou que a maioria das mortes relacionadas ao tumor ocorreram poucos meses após os procedimentos cirúrgicos, sendo que 8,8% das mortes ocorreram no primeiro ano, estando relacionados ao mau estado clínico e neurológico dos pacientes por ocasião da indicação cirúrgica (20). Comparativamente, Curry et al. (21) relataram 2,3% de mortalidade e 21,2% de transferência dos pacientes para hospitais de retaguarda para acompanhamento clínico e reabilitação a longo prazo. O risco de morte relacionada ao tumor reduziu drasticamente após dois anos do procedimento cirúrgico em pacientes com GI. Embora muitos pacientes tivessem apresentado recorrência e tenham sido submetidos a tratamento adicional, a maioria destes pacientes morreram por causas não relacionadas ao meningioma.

O benefício de procedimento cirúrgico agressivo para reduzir a recorrência tumoral tem sido debatido na literatura (22). Em nossa série, o intervalo livre de

recorrência não teve impacto significativo na sobrevida ou nos desfechos clínicos em pacientes com meningiomas GI. No entanto, a recorrência foi seguida de morte em todos os pacientes com tumores GII ou GIII. Os meningiomas localizados na convexidade, sem o envolvimento do seio venoso, se associaram a menor risco de recorrência, cerca da metade do risco em comparação com os tumores em outros locais. Notou-se que todos os pacientes com GII com sobrevida maior que dez anos apresentavam tumores na convexidade, sugerindo que uma ressecção completa pode ser mais determinante que o grau histológico na evolução tumoral (23).

A radiocirurgia, uma modalidade terapêutica menos invasiva que a cirurgia, foi o tratamento primário para a recorrência, o que provavelmente explica, em parte, o menor impacto da recorrência na incidência de mortalidade dos pacientes em nossa série, corroborando os dados da literatura (24). Em contraste ao observado em pacientes com meningiomas GI, 94,1% das mortes dos pacientes com meningiomas GII e GIII foram relacionadas à evolução tumoral ou ao tratamento, independentemente do tempo de seguimento.

Meningiomas GI foram proporcionalmente mais frequentes que GII e GIIII na base do crânio em comparação à convexidade na presente coorte, o que diferiu de resultados publicados anteriores evidenciando predomínio de meningiomas malignos na base do crânio (25, 26). Além disso, entre os subtipos histológicos de GI, os subtipos meningotelial e transicional foram mais frequentes na base do crânio, com frequência ligeiramente maior do que o subtipo meningotelial nessa região do que na convexidade. Curiosamente, o subtipo meningotelial comumente apresenta a mutação *AKT1* (27), e a localização deste tipo de tumor também foi relatada recentemente como mais predominante na base do crânio (25). A origem embriológica distinta das meninges que envolvem o sistema nervoso central pode ser uma explicação para as diferenças nas distribuições histológicas. Nos estágios iniciais da embriogênese, o mesênquima primitivo ao redor do tubo neural se condensa para formar a membrana cerebral primária (28, 29). O periósteo do osso frontal e as células do septo nasal são derivados das células da crista neural que contribuem para o desenvolvimento da foice do cérebro e dura-máter adjacente (28, 29). Foi relatado que as meninges ao redor do tronco cerebral surgem do mesoderma cefálico, enquanto as meninges telencefálicas provavelmente surgem das células da crista neural (30-33). Consequentemente, as meninges que cobrem o tronco

encefálico e a medula espinhal surgem de uma linhagem embriológica claramente diferente das meninges da convexidade cerebral. Esta diferença embriogênica também pode estar implicada na predominância observada do subtipo meningotelial no neuroeixo central (29).

Este achado da preponderância de meningioma GI na base do crânio tem uma implicação no manejo neuro-oncológico porque os tumores nesta localização apresentam desafios para a ressecção. Portanto, ao invés de objetivar a ressecção completa do tumor, uma diminuição do efeito de massa (12) pode ser suficiente sem qualquer impacto adicional na mortalidade geral ou sobrevida livre de progressão.

Os meningiomas intraventriculares são de fato tumores extremamente raros, representando 0,5-5% de todos os meningiomas intracranianos (34, 35), e menos de 2% na presente coorte. Eles surgem tanto do estroma do plexo coróide ou da tela coróide e não apresentam nenhuma correlação dural (36). Poucos dados estão disponíveis na literatura sobre seu subtipo histológico (34, 37-41). Embora o número total de meningiomas ventriculares na presente série seja pequeno (n = 7), encontramos mais meningiomas atípicos nesta região (n = 4), enquanto os tipos meningotelial e fibroso foram previamente relatados como mais frequentes nesta localização (34, 42). De fato, entre os três meningiomas intraventriculares GI da nossa coorte, 2 eram do subtipo fibroso.

Além disso, o sexo masculino foi associado a um maior risco de malignidade consistente com vários estudos publicados anteriormente (43-46). Esse achado reforça a necessidade de manejo neuro-oncológico mais agressivo em pacientes do sexo masculino com terapias adjuvantes após a cirurgia, como radioterapia, e com acompanhamento mais regular.

Impacto da faixa etária, localizações e apresentação clínica na recorrência

PUBLICAÇÃO 1

Título	Comprehensive analysis of meningioma in the first two decades of life: A systematic review		
Autores	Benedito Jamilson Araujo Pereira, Antonio Nogueira de Almeida, Paulo Henrique Pires de Aguiar, Wellingson Silva Paiva, Manoel Jacobsen Teixeira, Suely Kazue Nagahashi Marie		
Revista	Neurochirurgie		
Submetido	11/04/2019	**Aceito**	15/10/2019
Citação completa	Jamilson Araujo Pereira B, Nogueira de Almeida A, Henrique Pires de Aguiar P, Silva Paiva W, Jacobsen Teixeira M, Kazue Nagahashi Marie S. Comprehensive analysis of meningioma in the first two decades of life: A systematic review. Neurochirurgie. 2020 Feb;66(1):36-40. doi: 10.1016/j.neuchi.2019.10.007.		
Fator de Impacto	0.948		
Citações	Scopus: 1; Web of Science: 1; Google scholar: 1		

Neurochirurgie 66 (2020) 36–40

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

General review

Comprehensive analysis of meningioma in the first two decades of life: A systematic review

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ARTICLE INFO

Article history:
Received 24 June 2019
Received in revised form 19 October 2019
Accepted 20 October 2019
Available online 3 December 2019

Keywords:
Juvenile population
Histopathology
Meningioma subtype

ABSTRACT

Purpose. – To evaluate the relationship between meningioma histological subtype and tumor site in under-20 year-olds.
Methods. – A review of the literature on meningioma during the first 2 decades of life was carried out through a Medline search up to February 2019. To evaluate the adult population, a cross-sectional study was conducted on patients operated on between 2000 and 2014 in a single institution. Exclusion criteria comprised: series reports and papers that lacked detailed description of clinical findings, neuroimaging confirmation of tumor location, and/or at least 5 years' follow-up.
Results. – One hundred and seven manuscripts were included, for 365 under-20 year-old patients: 200 male, and 164 female. Histopathology found 197 cases (53.9%) of WHO grade I meningioma, with predominance of meningothelial (41.1%) and transitional (30.9%) subtypes; 123 (33.7%) grade II, and 45 (12.3%) grade III. For 65 (18.25%) of the 356 cases, recurrence was documented, with only 24 deaths (6.7%).
Conclusion. – Meningioma in this population presented 2 differences compared to the adult population: male predominance, and high incidence of atypical meningioma. Surgery was the primary treatment. Adjuvant radiotherapy is controversial in the literature.

1. Introduction

Meningioma is the most common benign intracranial tumor, accounting for approximately one-third of all CNS tumors [1], with annual incidence of approximately 6 per 100,000 [2]. Meningioma is more commonly diagnosed in adults than in younger individuals; meningioma in under-20 year-olds accounts for less than 5% of all pediatric brain tumors and less than 2% of all meningiomas [3,4].

Although 80% of meningiomas show benign clinical behavior and can be cured by surgical resection alone, about 20% recur after resection and need additional treatment such as further surgery, radiotherapy or systemic chemotherapy [5,6]. Histopathological assessment aims to identify patients at risk of recurrence [7]. There are fewer publications regarding under-20 year-olds, which complicates standardization of therapeutic proposals for patients who differ from the adult population.

According to the 2016 WHO [8] classification of meningioma, grade I (GI) is considered benign. Nine histological subtypes are included in GI: meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich and metaplastic. Grade II (GII) tumors, which are more aggressive than GI, include the clear cell, chorodoid and atypical subtypes. Papillary, rhabdoid, and anaplastic meningiomas are grade III (GIII), the most malignant category [9].

Several risk factors for meningioma in the juvenile population have been identified, such as ionizing radiation exposure, which may cause DNA mutations either directly or indirectly via free radicals, leading to tumorigenesis [10–13].

Several issues remain controversial in regard to whether any specific histopathological subtype, age and anatomic tumor location might be taken as markers for prognosis and determination of therapeutic strategies. Through a broad review of all detailed cases published on the subject, this study seeks to fill this gap. The objective is to assess the impact of histological subtype and the tumor site in under-20 year-olds.

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https://doi.org/10.1016/j.neuchi.2019.10.007
0028-3770/

2. Method

A review of the literature on under-20 year-olds was conducted through a Medline search of articles up to February 2019. For selection, reports of series of meningioma in under-20 year-olds were included, and papers lacking detailed description of clinical findings, neuroimaging confirmation of tumor location and/or follow-up of at least 5 years were excluded.

The retreatment interval was defined as the time between primary surgery and the first subsequent treatment (radiotherapy or new surgical procedure). This concept was employed to avoid subjectivity in differentiating tumor remnants from scars located near the resection site. Degree of surgical resection was defined according to the Simpson classification [14]: gross total resection (GTR) (grades I and II) or subtotal resection (STR) (grades III, IV, and V).

Meningiomas were graded on the 2007 WHO criteria [5], and histological subtypes were determined according to WHO 2016 [8]. Tumor sites were grouped into 3 areas:

- convexity, including the skull region;
- skull base;
- intraventricular.

The convexity area was defined as the dura mater of the calvarium, and also included the falcotentorial area, comprising falx, tentorium, and the calvarium areas containing the sagittal, transverse and sigmoid sinuses. The skull base was defined as the surroundings of the carotid artery and cranial nerves I to VI. The intraventricular petroclival area was defined as the region in the posterior fossa surrounding the petrous bone or lower segment of the clivus, regions related to cranial nerves VII to XII and the vertebral artery and cerebellopontine angle, and the cistern was defined as the triangular subarachnoid space between the anterior surface of the cerebellum and the lateral surface of the pons containing cranial nerves VII and VIII and the anterior-inferior cerebellar artery [15].

3. Results

The systematic review retrieved 371 manuscripts, of which 264 were excluded due to incomplete or inconsistent Abstract, incomplete description of the clinical findings, or insufficient follow-up. The remaining 107 manuscripts were analyzed (Fig. 1), totaling data for 365 patients under 20 years of age: 200 male, 164 female; mean age, 11.5 ± 4.9 years. Meningiomas were located in the brain convexity (159; 44%), skull base (104; 29%), spinal column (60; 16%) or ventricle (41; 11%). Histology found 197 (54%) GI, with predominance of meningothelial (41%) and transitional (31%) subtypes; 123 (34%) GII; and 45 (12%) GIII. Extent of surgical resection according to Simpson score was available in 315 cases: GTR in 279 cases (89%), STR in 36 (11%). Tumor recurrence occurred in 65 (18%) of the 356 cases with retrievable information about this parameter. Only 24 deaths (7%) were recorded out of the 356 cases with evaluation of this parameter (Table 1).

3.1. Radiation-related meningioma

The 53 cases of radiation-related meningioma involved 32 males and 21 females, with a mean age of 12.4 ± 4.7 years. Tumors were located in the brain convexity (42; 81%), skull base (8; 15%) or spinal column (2; 4%). Histology revealed 31 cases (58%) of GI, with predominance of meningothelial (48%) and transitional (26%) subtypes; 15 GII (28%); and 7 GIII (13%). Tumor recurrence occurred in 14 (30%) out of the 46 cases with information about this parameter. There were only 4 deaths (9%).

4. Discussion

Meningiomas in young patients differ significantly from their adult counterparts [16]. Intracranial meningiomas constitute a strikingly low (0.4% all brain tumors in juvenil population; 4.6% all brain meningiomas) percentage of brain tumors in juveniles, whereas they are the most common benign brain tumor in adults [17]. Presentation also differs from that of adults, with male predominance, cystic changes, higher frequency of neurofibromatosis and high-grade meningioma, and lack of dural attachment [18].

Ravindranath et al. suggested that the higher rate of meningioma in the first 2 decades of life in males may be due to the absence of sex hormones [19]. In the adult population, presence of estrogen and progesterone receptors was reported in various grades of meningiomas [20,21] and these hormones play an important role in stimulating meningioma cell proliferation [22]. Interestingly, we observed peaks of meningioma incidence in young patients and also in the sixth decade, coinciding with respectively an increase and a decrease in sex hormone levels. The impact of hormone fluctuation has not been fully explored, and very few studies assessed postmenopausal status in relation to implementation and duration of hormone replacement therapy [23]. Hormonal influence is also interesting in the male population, as higher average body mass index (BMI) and higher obesity rates were reported in male meningioma patients [24]. As expected, obese male meningioma patients presented higher rates of postoperative complications such as deep venous thrombosis, pulmonary embolism and fever than non-obese patients.

Obesity has been shown to increase serum estradiol and insulin-like growth factor (IGF), which in turn links obesity to carcinogenesis [25,26]. Additionally, male gender is associated with higher risk of malignancy [27–30]. These findings reinforce more aggressive neuro-oncological management, with postoperative adjuvant therapy (e.g., radiotherapy), and more regular follow-up for male patients.

The relatively high incidence of GII-GIII meningioma in under-20 year-olds, at both the skull base and the convexity, contrasted with adults, in whom malignant meningioma is predominantly found at the skull base [7,31].

In GI, meningothelial and transitional subtypes were more frequently found at the skull base, with a slightly higher frequency of the meningothelial subtype in both younger and adult populations, corroborating previous reports [7]. The distinct embryological origin of the meninges that involve the central nervous system might explain the differences in histological distributions. In the early stages of embryogenesis, the primitive mesenchyme around the neural tube condenses to form the primary meninx [32,33]. The frontal bone periosteum and nasal septum cells derive from neural crest cells that contribute to the development of the falx cerebri and adjacent dura mater [32,33]. The meninges around the brainstem arise from the cephalic mesoderm, whereas the telencephalic meninges probably arise from neural crest cells [34–37]. Thus, the meninges covering the brainstem and spinal cord arise from a clearly different embryological lineage than the meninges of the cerebral convexity. A preponderance of GI meningioma in the skull base also has implications for neuro-oncological management, as tumors in this location present challenges for resection. Instead of aiming for complete tumor resection, a decrease in mass effect [38–40] may be sufficient, without impairing overall mortality or progression-free survival.

Intraventricular meningioma is defined as meningioma originating from the choroid plexus and growing strictly within the ventricles [41,42]. It is a rare location [43] and accounts for only 0.5–3% of all intracranial meningiomas [44]. The tendency for meningioma to grow within the ventricles is explained by the inclusion of arachnoid cells in the choroid plexus and velum

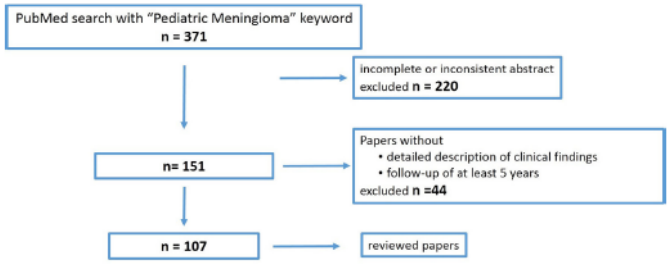

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study flow diagram.

Table 1
Tumor sites and histological subtype.

	Convexity		Skull base		Ventricular		Spinal		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Grade I	74	20.27	65	17.80	27	7.39	32	8.76	197	53.97
Histological subtype										
Meningothelial	33	9.04	26	7.12	5	1.36	16	4.49	81	22.19
Transitional	22	6.02	18	4.93	13	3.56	9	2.46	61	16.71
Fibrous	7	6.32	6	1.64	9	2.45	1	0.27	24	6.57
Microcystic										
Angiomatous			2	0.54						
Psamomatous			10	2.73			6	1.64	16	4.38
Secretory	1	0.27							1	0.27
Others	12	3.28							12	3.28
Grade II	60	7.08	32	8.76	4	1.0	26	7.12	123	34.56
Grade III	25	6.84	8	2.19	10	2.73	2	0.54	45	12.64
Total	159	43.56	105	28.76	41	11.23	60	16.43	365	100

interpositum [45,46]. In under-20 year-olds, the incidence of intraventricular meningiomas is 5 times that in the adult population.

Molecular alterations in meningioma in the first decades of life notably concern AKT1E17 K and NF2. AKT1E17 K mutations occur in specific subsets of meningioma, with highest incidence in spinal and basal WHO grade I meningothelial and transitional meningiomas [47]. Pediatric and/or NF2-associated meningiomas are much less common than their sporadic counterparts in adults [48]. Pediatric NF2 patients are much more likely to have meningioma than older NF2 patients [49]. The NF2 association with pediatric meningioma is clear in other series, with rates of 7–41% [45,50–53].

Several types of radiation-induced tumor have been reported in pediatric patients. Meningioma is the second most common radiation-induced tumor in children [54], and can develop even after low-dose radiation and has distinct characteristics from those of primary meningioma [55]. Cahan et al. [56] suggested 4 criteria for defining radiation-induced tumor. Firstly, the tumor must be located in a previously irradiated region where there was no evidence of tumor prior to irradiation. Secondly, there must be sufficient latency, generally of several years, between irradiation and tumor onset. Thirdly, the tumor must have distinct histologic characteristics from the primary tumor. And fourthly, the patient must have no genetic predisposing factor that could contribute to tumor onset.

Modan et al. retrospectively reviewed nearly 11,000 patients who had undergone radiation for tinea capitis as children [13], and found a 4-fold higher incidence of meningioma. Meningioma typically occurs beyond 10 years after treatment; a median interval of more than 20 years from primary cancer diagnosis to meningioma diagnosis was reported in large cohort studies of childhood cancer survivors [57,58]. Furthermore, the excess risk does not seem to plateau over time [59]. Meningioma risk appears to increase with increasing radiation dose [58,60], although the role of exposed cranial volume has not been studied and should be considered in future studies. Some studies reported that the lower the age at childhood cancer diagnosis, the higher risk of meningioma [61–63], which may be due to higher sensitivity to radiation, as observed in other tissues (e.g., thyroid gland) [63]. However, studies that directly addressed this hypothesis, evaluating meningioma risk in childhood cancer survivors [58,60] and children treated for tinea capitis [64], found no clear association between radiation dose and age at exposure. Of all chemotherapy drugs evaluated in 2 large cohorts of childhood cancer survivors, platinum agents and intrathecal methotrexate were the only ones associated with increased risk of meningioma [61,62]; however, these findings have not been replicated. Radiation-induced meningioma tends to be more aggressive, with higher incidence of recurrence, and is more likely to be multifocal than sporadic [45]. Analyzing the data for radiation-induced meningioma in particular, we found a higher rate of recurrence compared to sporadic meningioma (30.4% vs. 17%), which may also be due to a higher proportion of atypical meningiomas in radiation-induced meningioma. Nevertheless, mortality was similar in both groups (8% vs. 6.5%), probably reflecting a similar success rate of total tumor resection in both groups (94.7% vs. 88%).

Review of these cases revealed no obvious differences from histologically benign cases associated with favorable clinical behavior (data not shown), although detailed data on extent of resection was lacking. Other authors reported that the great majority of benign pediatric meningiomas showing recurrence had been subtotally resected [51,65–67]. Aggressive variant morphology was most often encountered focally, although 4 cases involved papillary or clear-cell primaries. This is consistent with the younger mean age of patients with these 2 variants [68,69]. In contrast, rhabdoid and chordoid meningioma have mean ages closer to that of patients with typical meningioma [70,71]. Several authors advocate

radiotherapy to prevent local recurrence after stereotactic radiosurgery (SRS), but others consider the procedure ineffective and liable to induce radiation-induced toxicity [72–75]. The efficacy of radiotherapy for local control of pediatric spinal meningioma should be further investigated; however, if the regrowth is unresectable and neurological functions progressively worsen, then radiation therapy should be attempted, and especially SRS such as CyberKnife, which can minimize the risk of radiation-related complications. Similarly, there is little evidence that chemotherapy is effective for this type of tumor [76]. Larger and much faster growth and malignant transformation, along with a higher relapse rate, are blamed for the poorer overall prognosis for meningioma in children than in adults [77].

Although this study had a large sample size, limitations should be borne in mind. Information on the extent of tumor resection was obtained following the descriptions in the article, as it was not always specified how degree of resection was assessed (on imaging, or only on surgical findings); most of the articles did not present details of this topic.

5. Conclusions

Patients under 20 years of age presented 2 distinct characteristics compared to the adult population: male predominance, and a high incidence of atypical meningioma. The histological subtype distribution was similar in both groups, with the meningothelial subtype more prevalent in the skull base. The age peaks of meningioma incidence corresponding to hormonal variation in both the juvenile and adult groups may motivate further future studies to address the hormonal impact in meningioma tumorigenesis. Surgery was the primary treatment; adjuvant radiotherapy is still controversial in the literature.

Funding

None.

Ethical approval

This study was approved by our Institutional Review Board under registration n°CAPPESq # 200/05. All authors agreed to the publication guidelines of Neurochirurgie.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neuchi.2019.10.007.

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PUBLICAÇÃO 2

Título	Natural history of intraventricular meningiomas: systematic review		
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Revista	Neurosurgical review		
Submetido	30/04/2018	**Aceito**	02/08/2018
Citação completa	Pereira BJA, de Almeida AN, Paiva WS, de Aguiar PHP, Teixeira MJ, Marie SKN. Natural history of intraventricular meningiomas: systematic review. Neurosurg Rev. 2020;43(2):513-23. doi: 10.1007/s10143-018-1019-0.		
Fator de Impacto	2.532		
Citações	Scopus: 6; Web of Science: 5; Google scholar: 12		

Neurosurgical Review
https://doi.org/10.1007/s10143-018-1019-0

REVIEW

Natural history of intraventricular meningiomas: systematic review

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Received: 30 April 2018 / Revised: 23 July 2018 / Accepted: 2 August 2018

Abstract
Review the data published on the subject to create a more comprehensive natural history of intraventricular meningiomas (IVMs). A Medline search up to March 2018 using "intraventricular meningioma" returned 98 papers. As a first selection step, we adopted the following inclusion criteria: series and case reports about IVMs, as well as papers written in other languages, but abstracts written in English were evaluated. Six hundred eighty-one tumors were evaluated from 98 papers. The majority of the tumors were located in the lateral ventricles (602–88.4%), fourth ventricle (59–8.7%), and third ventricle (20–2.9%). These tumors accounted for a mortality rate of 4.0% (25 deaths) and a recurrence rate of 5.3% (26 recurrences). The majority of the tumors were grade I (89.8%) and consisted of the following subtypes: fibrous, 39.7% ($n = 171$); transitional, 22.0% ($n = 95$); meningothelial, 18.6% ($n = 80$); angiomatosus, 3.2% ($n = 14$); psammomatous, 2.6% ($n = 11$); and others, 13.9% ($n = 60$). Forty-five patients (7.4%) presented with grade II (GII) tumors, and 17 patients (2.8%) presented with grade III (GIII) tumors. These tumors follow the histopathological distribution of meningiomas in general, with the exception of the higher prevalence of the fibrous subtype, possibly due to its embryonic origin. Recurrence and mortality were lower than in other localizations likely due to a complete surgical resection rate than in the convexity and skull base, which suggests that GTR is the gold standard for the management of IVMs.

Keywords Ventricular meningioma · Prognostic · Surgery

Introduction

Meningiomas are usually benign, solid tumors with a classic appearance on CT scans and MRIs that account for approximately 13–40% of intracranial neoplasms, making them the second most common intracranial tumors in adults with an incidence of 1.5–5.5 per 100,000 [1–5]. Intraventricular meningiomas (IVMs) show clinical and pathological features that differentiate them from meningiomas in other locations, such as low prevalence, as they account for only 0.5–3% of all meningiomas and 9.8 to 14% of all intraventricular tumors. Twenty percent of IVMs were located in the lateral ventricle [6, 7], with no dural attachment [8] hindering neurosurgical management due to their proximity to the visual pathways, which may potentially cause visual field defects in the surgical approach [9, 10].

Patients with a lateral ventricular tumor generally present with a secondary trapped ventricle because of the mass effect, and patients with third or fourth IVMs also present with hydrocephalus [11].

Considering the rarity of IVMs, we compiled all the results of the reported series and case reports in the literature to form a more comprehensive natural history of these tumors.

Methods

A Medline search up to March 2018 using the key phrase "intraventricular meningioma" returned 98 papers; we based our revision on this initial corpus. As a first selection step, we adopted the following inclusion criteria: series and case reports about IVMs, as well as papers written in other languages, but abstracts written in English were evaluated. Ninety-eight papers fulfilled the above criteria (two were reviews of the literature with all cases of meningiomas located

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Published online: 15 August 2018

in the fourth ventricle) [see Fig. 1 for the PRISMA study flow diagram]. These papers gathered data from 681 patients, on whom the present analysis of natural history and neuro-oncological management of IVMs was based.

In this paper, the recurrence-free interval is considered the time between the first surgery and the first subsequent treatment (radiotherapy or a new surgical procedure). We used this definition to avoid subjectively differentiating tumor remains from scars near the sites of resection.

According to the World Health Organization (WHO), the age groups of the population are defined as follows: young people are under the age of 15, adults are those aged 15–64, and the elderly are those over 65 years old [12].

Results

A total of 681 tumors were evaluated (361 from female patients and 245 from male patients; 1.47 female/1.0 male ratio; 75 patients reported no gender), the majority were located in the lateral ventricles (602–88.4%). Among the 681 tumors evaluated, 608 (89.3%) had a histopathological description and 546 patients (89.8%) presented with GI tumors, with predominance of the fibrous subtype (39.7%). In 45 patients (7.4%) presented with grade II tumors, and 17 (2.8%) presented with GIII tumors. Throughout the review, we were able to evaluate the degree of tumor resection in 571 patients (83.8%), with gross total resection (GTR) in 541 cases (94.7%). These data were the results of 98 manuscripts from worldwide centers up to March 2018 that were selected for the present analysis. We managed to analyze studies from all continents (see Table 1).

Age The confirmed ages of the included patients at diagnosis ranged from 1 to 81 years (mean 42.2 ± 8.2 years old). The histopathological distribution, recurrence, and mortality rates related to each age group are listed in Table 2.

Mortality Among the cases reported in the literature, 625 presented reports of a disease, and in total, we observed 25 deaths (4.0%). The period of the deaths was divided into two phases. The first period concentrated in the first month after neurosurgical management included 11 deaths (44%). Complications related to the procedure, such as postoperative hematoma, were responsible for more of the half of these deaths (54.5%). Other complications, such as pulmonary embolism after the surgical procedure, clinical deterioration, and diseases such as bronchopneumonia, were responsible for another five deaths in this period (45.5%). After this period, we observed that in nine cases (36%), the deaths followed another pattern related to other clinical problems or even the progression of the disease. Surgical site infection occurred in two cases (22.2%); two (22%) cases presented clinical deterioration, one presented liver metastasis, and the other presented clinical deterioration after malignancy of the primary fibrous tumor. One case presented a sporadic episode of pulmonary embolism after 4 months. The causes of the other four deaths had not been reported. In four cases, the time between procedure and death was not reported. One patient presented with a bleeding tumor and died before any treatment (see Table 3).

Recurrence Among the patients observed in this review, 494 presented information about tumor recurrence, and 26 (5.3%) tumors recurred. The recurrence period ranged from 3 to 84 months between the surgical procedure and the recurrence, with an average of 26 months. In three cases, we observed recurrence with tumor malignancy increasing from GI to GII or GIII (see Table 4).

Discussion

According to the 2016 WHO classification of central nervous system tumors [105], meningiomas are classified into three grades: I, II, and III. Grade I meningiomas are typical or benign, and they represented 88–94% of all meningiomas [106];

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study flow diagram

Table 1 Literature review

Author	Year	Country	Age	Gender		Ventricle			GI	GI Subtype						GII	GIII	GTR	STR	Rec	Death
				M	F	Lat	III	IV		*F*	*T*	*M*	*P*	*A*	Others						
Tukanowicz, A [13]	1958	USA	44*	3	5	8	0	0	8	7	nr	nr	nr	nr	1	0	0	8	nr	0	5
Fornari, M [14]	1981	Italy	nr	4	14	18	0	0	18	5	0	0	0	0	13	0	0	18	0	0	4
Guideti, B [15]	1985	Italy	32*	7	12	19	0	0	19	17	nr	1	1	nr	nr	nr	nr	19	nr	0	0
Hosaka, Y [16]	1985	Japan	69	1	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0
Kleinschmidt [17]	1986	Germany	34	1	0	1	0	0	1	0	1	0	0	0	0	0	0	1	0	1	1
Criscuolo, CR [3]	1986	UK	45.5*	2	8	10	0	0	9	1	0	5	0	3	0	0	1	10	0	1	1
Shirasaka, A [18]	1987	Japan	2	1	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0
Kamyia, K [19]	1989	Japan	67	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1
Byard, RW [20]	1989	Australia	9*	1	1	2	0	0	2	2	0	0	0	0	0	0	0	0	0	0	0
Jelinek, J [21]	1990	USA	nr	4	5	9	0	0	9	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Conforti, P [22]	1991	Italy	nr	nr	nr	10	0	0	nr	nr	nr	nr	nr	nr	nr	nr	nr	10	0	0	1
Caner, H [23]	1992	Turkey	40.6*	3	3	6	0	0	6	2	nr	3	nr	1	0	0	0	6	0	0	0
Ceylan, S [24]	*1992*	*Turkey*	*36.8**	*11*	*14*	*0*	*0*	*25*	*24*	*7*	*3*	*6*	*1*	*0*	*7*	*1*	*0*	*19*	*6*	*nr*	*nr*
Yasuma, Y [25]	1993	Japan	44	1	0	1	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0
Lang, I [26]	1994	UK	64	0	1	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0
Sgouros, S [27]	1994	UK	6	1	0	0	1	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Pen, WC [28]	1995	Hong K.	34	0	1	1	0	0	1	1	0	0	0	0	0	0	1	1	0	1	0
Couillard, P [29]	1995	Saudi A.	26	0	1	1	0	0	nr	nr	nr	nr	nr	nr	nr	nr	nr	0	0	0	0
Murai, Y [30]	1996	Japan	39	0	1	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0
Pau, A [31]	1996	Italy	9	1	0	0	1	0	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Tarik, K [32]	1997	Japan	37	1	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Kloc, C [33]	1998	Poland	13.5*	1	1	2	0	0	2	0	0	2	0	0	0	0	0	2	0	0	0
Terada, T [34]	1999	Japan	58	0	1	1	0	0	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Majós, C [35]	1999	Spain	34.5*	2	0	2	0	0	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Curry Jr., W [36]	2001	USA	36	0	1	1	0	0	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Lee, E [37]	2001	Korea	43	0	1	1	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0
Nakamura, M [10]	2003	Germany	47.1*	8	8	13	1	2	15	6	1	6	1	1	0	1	0	15	1	0	0
Chen, N [38]	2003	Taiwan	74	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0
Darwish, B [39]	2004	New Z	53	0	1	1	0	0	0	0	0	0	0	0	0	1	0	1	0	1	0
Marrelo, CE [40]	2005	Spain	5	0	1	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Arima, T [41]	2005	Japan	37	0	1	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Buhl, R [42]	2005	Germany	51	2	3	5	0	0	5	1	1	2	0	0	1	0	0	nr	nr	nr	nr
Bertanlaffy, A [1]	2006	Austria	44*	5	11	16	0	0	13	nr	4	8	nr	nr	1	3	0	14	1	0	0
Tokunaga, K [43]	2006	Japan	57	0	1	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0
Li, XZ [44]	2006	China	nr	nr	nr	64	0	0	63	35	3	0	0	0	25	0	1	64	0	nr	0
Liu, M [45]	2006	China	39*	8	17	24	0	1	24	11	1	8	1	2	0	1	0	25	0	0	0
Bathoe, HS [46]	2006	India	nr	9	3	9	1	2	12	1	0	4	1	5	1	0	0	11	1	0	1
Hackyemez, B [47]	2006	Turkey	57	0	1	1	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0
Lingdoh, BT [48]	2007	India	34.6*	4	5	7	0	2	9	3	4	2	0	0	0	0	0	8	1	0	0
Shogan, P [49]	2007	USA	71	0	1	1	0	0	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Wang, X [50]	2007	China	44*	20	31	51	0	0	nr	nr	nr	nr	nr	nr	nr	nr	nr	48	3	0	0
Costa, L [51]	2007	Brazil	45	1	0	1	0	0	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Romeike, BF [52]	2007	Germany	57	0	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1
Mcmaster, J [53]	2007	Australia	55	0	1	1	0	0	1	1	0	0	0	0	0	0	1	1	0	1	0
Shintako, M [54]	2007	Japan	61	0	1	1	0	1	1	0	1	0	0	0	0	0	1	2	0	0	0

Table 1 (continued)

Author	Year	Country	Age	Gender		Ventricle				GI Subtype											
				M	F	Lat	III	IV	GI	*F*	*T*	*M*	*P*	*A*	Others	GII	GIII	GTR	STR	Rec	Death
Gonzales [55]	2008	Spain	41.6*	4	6	10	0	0	8	1	0	6	1	0	0	1	0	9	0	0	1
Fulkerson, D [56]	2008	USA	54	1	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0
Cassereau, J [57]	2008	France	50	1	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Kim, EY [58]	2009	Korea	36*	5	7	12	0	0	5	1	3	1	0	0	0	3	4	12	0	2	0
Menon, G [9]	2009	India	40.6*	5	10	15	0	0	14	nr	nr	nr	nr	nr	nr	1	0	14	1	2	0
Ney, D [59]	2009	USA	25	1	0	1	0	0	1	0	1	0	0	0	0	0	0	1	0	0	0
Kim, I [60]	2009	USA	51*	3	6	9	0	0	5	nr	nr	nr	nr	nr	nr	1	nr	nr	1	3	0
Mahory, A [61]	2009	India	45	1	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0
Eom, K [62]	2009	Korea	50	1	0	1	0	0	1	0	0	0	0	0	1	0	0	1	0	1	1
Eom, K [63]	2009	Korea	42	0	1	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Dulai, MS [64]	2009	USA	7	0	1	1	0	0	1	0	0	0	0	0	1	0	0	1	0	0	0
Garcia, M [65]	2009	Spain	44	1	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	1	1
Nayar, M [11]	2010	USA	40.2*	2	11	13	0	0	12	nr	nr	nr	nr	nr	nr	1	0	13	0	0	0
Deb, P [66]	2010	India	45	1	0	1	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0
Cleary, C [67]	2010	Ireland	11	0	1	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Vuckovic, V [68]	2010	Serbia	51	1	0	1	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0
Baroncini, M [69]	2011	France	52*	17	23	40	0	0	38	nr	nr	nr	nr	nr	nr	1	1	nr	nr	Nr	0
Fu, Z [70]	2011	China	46	0	1	1	0	0	1	0	1	0	0	0	0	0	0	1	0	0	0
Silva, D [71]	2011	Brazil	44	1	0	1	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0
Zanini, MA [72]	2011	Brazil	47.8*	3	3	6	0	0	6	4	0	1	1	0	0	0	0	6	0	0	0
Lunardi, P [73]	2011	Italy	68	0	1	1	0	0	1	0	0	1	0	0	0	0	0	0	1	0	0
Kim, H [74]	2011	Korea	51	1	0	1	0	0	1	0	0	1	0	0	0	0	0	0	1	1	0
Takaushi, S [75]	*2012*	*Japan*	*47.5**	*9*	*6*	*0*	*0*	*15*	*15*	*6*	*4*	*3*	*0*	*0*	*2*	*0*	*0*	*nr*	*nr*	*nr*	*0*
Moyiadi, AV [76]	2012	India	3	0	1	1	0	0	1	0	1	0	0	0	0	0	0	1	0	0	0
El Ketani, N [77]	2012	Maroco	41	1	0	0	1	0	1	nr	nr	nr	nr	nr	nr	0	0	1	0	0	0
Ramraje, S [78]	2012	India	11.5*	0	2	0	0	2	2	1	0	1	0	0	0	0	0	2	0	0	0
Okechi H, [79]	2012	Kenya	7	0	1	1	0	0	1	0	0	0	0	0	1	0	0	1	0	0	0
Lin, T [80]	2012	Taiwan	54	0	1	1	0	0	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Odegaard, KM [8]	2013	Norway	52*	6	16	20	1	1	20	nr	nr	nr	nr	nr	nr	2	0	22	0	0	0
Neubacher, M [81]	2013	Germany	21	1	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Wang, Y [82]	2013	China	37	0	1	1	0	0	1	0	0	0	0	0	1	0	0	1	0	0	0
Nundkumar, N [83]	2013	USA	49.5*	0	2	2	0	0	2	2	0	0	0	0	0	0	0	2	0	0	0
Ma, J [84]	2014	China	42.8*	12	31	43	0	0	40	16	18	6	0	0	0	1	2	43	0	0	0
Qiu, L [85]	2014	China	45.5*	0	2	2	0	0	2	0	0	0	1	0	1	0	0	2	0	0	0
Giullion, M [86]	2014	Italy	46	1	0	1	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0
Tao, C [87]	2014	China	51	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1
Li,P [88]	2015	China	31.3*	7	6	0	13	0	11	3	3	1	0	0	3	2	0	8	5	0	1
Zhang, D [89]	2015	China	39	1	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Nanda, A [90]	2016	USA	47.3*	8	10	15	0	3	14	nr	nr	nr	nr	nr	nr	4	0	0	0	4	0
Dash, C [91]	2016	India	14.6*	4	2	5	1	0	6	4	2	0	0	0	0	0	0	6	0	0	0
Jack, AS [92]	2016	Canada	22	0	1	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Satyashiva, M [93]	2016	India	7	0	1	1	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0
Podromou, N [94]	2016	Greece	14	1	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Fujimaki, M [95]	2016	Japan	81	1	0	1	0	0	1	1	0	0	0	0	0	1	0	0	1	0	1
Sadashiva, N [96]	2016	India	48.5*	1	1	0	0	2	0	0	0	0	0	0	0	2	0	2	0	0	0

Table 1 (continued)

Author	Year	Country	Age	Gender		Ventricle			GI	GI Subtype						GII	GIII	GTR	STR	Rec	Death
				M	F	Lat	III	IV		*F*	*T*	*M*	*P*	*A*	Others						
Yuce, I [97]	2016	Turkey	20	1	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Grujicic, D [98]	2017	Serbia	43.6*	12	30	40	0	2	41	8	30	2	0	1	0	1	0	39	3	1	1
Singh, J [99]	2017	India	25	1	0	1	0	0	1	0	0	0	0	1	0	0	0	1	0	1	0
Sizdahkhani S [100]	2017	USA	35*	1	1	2	0	0	1	nr	nr	nr	nr	nr	nr	1	0	2	0	0	0
Muley, KD [101]	2017	India	7.5*	2	0	2	0	0	2	0	2	0	0	0	0	0	0	2	0	0	0
de Almeida, A [102]	2017	Brazil	36.4*	4	3	7	0	0	4	3	1	0	0	0	0	2	1	7	0	1	2
Li, Z [103]	2018	China	12.6*	18	12	30	0	0	28	13	10	5	0	0	0	1	1	26	4	3	1
Pricket, J [104]	2018	USA	49	0	1	1	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0
Total			42.2 ± 8.2	245	360	602	20	59	546	171	95	80	11	14	60	45	17	541	30	26	25

M, male; *F*, female; *Lat*, lateral ventricles; *III*, III ventricle; *IV*, IV ventricle; *GI*, meningioma grade I; *GII*, meningioma grade II; *GIII*, meningioma grade III; *F*, fibrous subtype; *T*, transitional subtype; *M*, meningothelial subtype; *P*, psammomatous subtype; *A*, angiomatosus subtype; *Others*, other subtypes; *GTR*, gross total resection; *STR*, subtotal resection; *NR*, not reported; *REC*, recurrence. *Mean age (years old)

Analysis of results:

I) Takeushi, S [75] reported the review with all cases of ventricular meningiomas. In the total sum of cases, two cases of the Lindgdoh [48] series and one case of the Liu [45] series were reduced, as these cases have already been counted in this review.

II) In this review, we added two papers (Ceylan, S and Takeushi, S) that talk about the same topic: meningioma of the fourth ventricle. Note that despite the review of the Takeushi's article, presents 27 cases, in our general account, we only computed 15, since 12 cases were selected in both reviews, being then taken from the analysis of that paper.

III) Although some series [8, 9, 11, 14, 15, 21, 23, 50, 69, 90] did not present, all the data for evaluation were included in this review due to some data relevant to the evaluation of at least some of the factors (resection grade, histological, recurrence and death rate).

IV) In a case report of Fujimaki, M, the pathological diagnosis of the intraventricular tumor was a mix of fibrous meningioma (WHO grade I) and anaplastic meningioma (WHO grade III).

V) In a case report of Zhang, D, the pathological diagnosis of the intraventricular tumor is an intraventricular meningioma and recurrent astrocytoma collision tumor.

VI) In a case report of Shintako, M, shown a case with anaplastic transformation and metastasis via the cerebrospinal fluid.

VII) The case reports of Macmarte, J and Wen PC show a case that recidivate with malignization.

VIII) In a case report of Romeike, BF, intraventricular meningioma was evaluated with fatal hemorrhage before the treatment.

IX) The case report of Li, XZ evaluated the abstract disponible on Pubmed.

Table 2 Distribution according age group. (Note that in some situations, the sum of the rows or columns of this table does not represent the same sum as in Table 1, but it must be considered that some papers lack information)

	Gender		Ventricle			GI Subtype									
Group	Male	Female	I/II	III	IV	GI	*F*	*T*	*M*	*P*	*A*	Others	GII	GIII	Recurrence	Death
Young	30	24	49	3	3	46	21	15	8	0	0	2	5	1	3	1
Adult	195	313	439	16	54	397	109	77	67	10	9	18	39	13	23	16
Elderly	4	2	6	0	0	3	2	0	1	0	0	0	1	2	0	2

M, male; *F*, female; *Lat*, lateral ventricles; *III*, III ventricle; *IV*, IV ventricle; *GI*, meningioma grade I; *GII*, meningioma grade II; *GIII*, meningioma grade III; *F*, fibrous subtype; *T*, transitional subtype; *M*, meningothelial subtype; *P*, psammomatous subtype; *A*, angiomatosis subtype; *Others*, other subtypes

atypical meningiomas are "intermediate-grade" malignancies (grade II) and accounted for 4.7–7.2% [107]. The anaplastic variant (grade III) is exceedingly rare, accounting for 1–3% of all meningiomas [108]. The results of this review demonstrated a similar distribution for IVMs; however, according to the new WHO classification [105], the proportion of IVMs will not increase much, as IVMs are not invasive.

Meningiomas are more common in women, and their incidence increases with age [2, 109, 110]. Data from the Central Brain Tumor Registry of the USA from 1985 through 1994 indicate that incidence rates for meningioma have remained fairly constant during this time [111] Meningiomas generally present a peak of incidence around the sixth decade [112] and, as previously mentioned, tend to be more prevalent as people get older. According to Jukich [111] the majority of patients are from the elderly population (51.4%), followed by the adult population (47.9%), and significantly fewer young population members (0.7%). The results of this revision show that the epidemiological profile of IVMs is different, being more common in the adult population, as IVMs are more symptomatic

Table 3 Death cases reported in this review

Author	Year	Gender	Localization	Histological subtype	Time after surgery	Cause
Tukanowicz [13]	1958	Male	Lateral	Fibroblastic	22 months	nr
		Male	Lateral	Fibroblastic	16 months	Abscess
		Male	Lateral	Fibroblastic	7 months	nr
		Female	Lateral	Fibroblastic	6 months	nr
		Female	Lateral	Meningothelial	5 days	Respiratory failure (pulmonary embolism?)
Fornari [14]	1981	nr	Lateral	nr	0 (intra-operative)	Hematoma in surgical site
		nr	Lateral	nr	1 day	Hematoma in surgical site
		nr	Lateral	nr	3 days	Hematoma in surgical site
		nr	Lateral	nr	9 days	Hematoma in surgical site
Kleinschimidt [17]	1985	Male	Lateral	Malignant	14 days	Bronchopneumonia (recidivate)
Criscuolo [3]	1986	nr	Lateral	Malignant	nr	Recurrence
Kamyia [19]	1989	Male	Lateral	Malignant	nr	Recurrence (6 months after surgery)
Conforti, P [22]	1991	nr	Lateral	nr	nr	nr
Bathoe, H [46]	2006	nr	Lateral	nr	Postoperative	Hematoma in surgical site
Romeike, BF [52]	2007	Female	Lateral	Fibrous	Presentation	Tumor bleeding
Gonzales [55]	2008	Female	Lateral	nr	3 days	Hematoma in surgical site
Eom KS [62]	2008	Male	Lateral	Malignant	1 month	Recurrence (clinical deterioration)
Garcia-conde [65]	2009	Male	Lateral	Atypical	7 months	Severe hepatic failure due livers metastases
Tao [87]	2013	Female	Lateral	Malignant	1 month	Pneumonia after lung metastasis resection
Li, P [88]	2015	Male	Third	Fibrous	3 months	Surgical site infection
Fujimaki [95]	2016	Male	Lateral	Fibrous	2 months	Malignant transformation/clinical deterioration
Grujicic [98]	2017	Male	Lateral	nr	25 days	Pulmonary embolism
Li [103]	2017	nr	nr	Malignant	nr	Recurrence
Pereira, BJ	2018	Male	Lateral	Transitional	7 months	nr
		Male	Lateral	Atypical	4 months	Pulmonary embolism

nr, not reported

Table 4 Recurrence cases reported in this review

Author	Year	Gender	Ventricle	Histological subtype	GTR	STR	RT	CT	Time after surgery
Kleinschimidt [17]	1986	Male	Lateral	Malignant	Yes	–	No	Yes	3 months
Criscuolo [3]	1986	nr	Lateral	Malignant	Yes	–	nr	nr	nr
Pen, W [28]	1995	Female	Lateral	Fibrous	Yes	–	No	No	5 years (malignant metaplasia)
Darwish, B [39]	1997	Female	Lateral	Atypical	Yes	–	No	No	4 months
Mcmaster, J [53]	2007	Female	Lateral	Fibrous	Yes	–	No	No	5 years
Kim, E [58]	2009	nr	Lateral	Atypical	Yes	–	Yes	No	5 years
		nr	Lateral	Malignant	Yes	–	Yes	No	2 years
Menon, G [9]	2009	nr	Lateral	Fibrous	–	Yes	No	No	2 years
		nr	Lateral	Fibrous	Yes	–	No	No	nr
Kim, I [60]	2009	nr	Lateral	nr	nr	nr	No	No	nr
		nr	Lateral	nr	nr	nr	No	No	nr
		nr	Lateral	nr	nr	nr	No	No	nr
Eom, K [63]	2009	Female	Lateral	Atypical	Yes	–	No	No	2 years
Garcia, M [65]	2009	Male	Lateral	Atypical	Yes	–	No	No	2 months
Kim, H [74]	2011	Male	Lateral	Meningothelial	–	Yes	No	No	3.5 years (metaplasia atypical)
Tao, C [87]	2014	Female	Lateral	Malignant	Yes	–	No	No	1 year
Nanda, A [90]	2016	Female	Lateral	Grade I	Yes	–	No	No	6 months
		Male	Fourth	Grade I	Yes	–	No	No	6 months
		nr	nr	nr	nr	nr	nr	nr	nr
		nr	nr	nr	nr	nr	nr	nr	nr
Grujicic [98]	2017	nr	nr	nr	–	Yes	No	No	1 year
Singh, J [99]	2017	Male	Lateral	Angiomatosus	Yes	–	No	No	6 month (metaplasia malignant)
Li [103]	2018	nr	nr	nr	nr	nr	nr	nr	1.2 year
		nr	nr	nr	nr	nr	nr	nr	1.5 year
		nr	nr	nr	nr	nr	nr	nr	7 years
Pereira, BJ	2018	Male	Lateral	Atypical	Yes	–	No	No	4 months

GTR, gross total resection; *STR*, subtotal resection; *RT*, radiotherapy; *CT* chemotherapy; *nr*, not reported

than meningiomas in other localities [46] and are therefore diagnosed more precociously. Of note, female gender prevalence in ventricular tumors is less evident than in meningioma series in general [112]. In young and elderly IVM patients, a predominance of males was observed but without impact on the outcome (higher death or recurrence rates).

Among all IVMs, 80% were in the lateral ventricle, 15% in the third ventricle, and 5% in the fourth ventricle [4, 10, 11], confirming the higher prevalence of IVMs in lateral ventricles. Conversely, IVMs were more prevalent in the fourth ventricle than in the third ventricle [75]. The observed distribution might be proportional to the extension of the choroid plexus, which is more present in lateral ventricles than in the fourth ventricle and, to a much smaller extent, in the third ventricle [113].

The distinct embryological origin of the meninges in the central nervous system might explain the differences in the meningioma's histological distributions. Meninges covering the brain stem and spinal cord arise from a clearly different embryological lineage than the meninges of the cerebral convexity. This embryogenic difference may also be implicated in the observed predominance of the meningothelial subtype in the central neuraxis, for example [114]. The embryological origin of ventricular tumors is completely different from those in other locations. Meningiomas arise from arachnoid cap cells, the specialized cells in arachnoid granulations. Similarly, IVMs arise from arachnoid cells present in the choroid plexus [46]. Third ventricle tumors arise from the tela of the velum interpositum, which is the space between the two layers of tela in the roof of the third ventricle that contains the posterior medial choroidal arteries and internal cerebral veins. IVMs also arise from choroids or interior tela choroidea [78].

Because of this embryological origin, we observed a greater proportion of fibrous subtypes (39.7% of all GI tumors) in IVMs, as already observed in other series and confirmed in this review. It is noteworthy that fibrous tumors show more aggressive behavior than other subtypes of GI tumors, as several case reports have shown. We observed more malignant metaplasia and tumor progression in originally fibrous tumors [53, 95], metastases in surgical site [61], carcinomatosis in

LCR [28], and other organs [56], associated with some presentations of intratumoral hemorrhage [16, 26, 30, 52], which were more frequent in this group of tumors, in addition to presenting a higher rate of mortality and tumor recurrence than the other tumors, as presented in Tables 2 and 3.

IVMs may be managed conservatively or treated with surgery or radiosurgery [11]. Radiosurgery may be recommended for patients who are not candidates for general anesthesia or who refuse surgical intervention although the intraventricular location causes distinct limitations for this technique [4].

Although the peculiar anatomy and its intimate relation to venous sinuses and important neuronal structures, such as visual pathways, represent a great challenge for surgeons, neurosurgical management is the best therapeutic option, as we have observed in the literature [55]. Because of their typically benign nature, complete microsurgical resection of IVMs is curative. Significant symptom resolution is common after removal of the lesion [115]. Despite technical difficulties, we found a high rate of GTR (95.1%) with a low mortality rate (4.0%).

Tumor vascular supply varies according to the exact location, but the main feeder vessels typically arise from choroidal arteries [116]. Careful preoperative planning of the optimal approach corridor and preservation of choroidal vessels and deep bystander veins minimize the chance of a major perioperative complication [116]. Mortality in most cases was related to hematomas in the surgical bed, probably related to a rich tumor vascularization associated with neovascularization. The benefit of aggressive surgeries to reduce recurrence and mortality has been debated in the literature [117], but ventricular tumors benefit more from GTR of the lesion probably more than tumors in other locations because ventricular lesions, in addition to the mass effect and compression of neural structures, promote obstruction of the cerebrospinal fluid circulation and, thereby, increase mortality and decrease the recurrence rate. Deaths within months after surgical procedures must be evaluated cautiously because many patients undergo the procedure in poor clinical and neurological states [118].

The recurrence rate (2.6%) is also low, compared to others [102], although most of the cases analyzed in this review come from case reports with a relatively short follow-up period, sometimes unreported [58, 60, 90, 103], associated with low frequency of recurrences.

Conclusion

These tumors follow the histopathological distribution of meningiomas in general, with the exception of the higher prevalence of fibrous subtypes, possibly due to their embryonic origin. The age distribution shows prevalence among the adult population. Recurrence and mortality rates are lower than in other localizations, most likely due to a complete surgical resection rate than convexity and skull base, which suggests that GTR is the gold standard for management of IVMs.

Limitations

Although this study had a large sample size, its limitations should be mentioned. Information on the extent of tumor resections were obtained following the description of the article, as each author classified the degree of resection (if through image examination, or only for surgical findings), was not specified in those articles. Most of the articles do not present detail of this topic, being a major impeding factor in this analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement This study was approved by our Institutional Review Board under the registration CAPPESq no. 200/05.

Informed consent All authors agree to the publication guidelines of the Neurosurgical Review

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PUBLICAÇÃO 3

Título	Neuro-oncological features of spinal meningiomas: Systematic review		
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Revista	Neurochirurgie		
Submetido	11/04/2019	**Aceito**	15/10/2019
Citação completa	Jamilson Araujo Pereira B, Nogueira de Almeida A, Henrique Pires de Aguiar P, Silva Paiva W, Jacobsen Teixeira M, Kazue Nagahashi Marie S. Neuro-oncological features of spinal meningiomas: Systematic review. Neurochirurgie. 2020; 66(1):41-4. doi: 10.1016/j.neuchi.2019.09.027.		
Fator de Impacto	0.948		
Citações	Scopus: 1; Web of Science: 0; Google scholar: 1		

Neurochirurgie 66 (2020) 41–44

Disponible en ligne sur ScienceDirect www.sciencedirect.com

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General review

Neuro-oncological features of spinal meningiomas: Systematic review

Caractéristiques neuro-oncologiques des méningiomes spinaux : revue systématique

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ARTICLE INFO

Article history:
Received 11 April 2019
Received in revised form 18 August 2019
Accepted 3 September 2019
Available online 28 October 2019

Keywords:
Spinal meningioma
Surgical modality
Recurrence
Mortality

ABSTRACT

Purpose. – Review the published data on spinal meningioma (SM) to create a more comprehensive picture of its natural history.
Methods. – A review of the published SM literature was carried out through a Medline search up to December 2018. The search using the keyword "spinal meningiomas" returned 248 papers and the parameters analyzed in our present study were examined in those publications. Papers without a detailed description of clinical findings, neuroimaging confirmation of the spinal tumor, minimum follow-up of 5 years, or a clear description of the clinical findings were excluded.
Results. – In the 24 manuscripts reviewed, 1811 (1450 females/361 males) patients with SM were analyzed. The thoracic spine (1181–64.6%) and cervical spine (394–22.7%) were the more prevalent levels. The psammomatous (27.8%) and meningothelial variants (25.2%) were the most prevalent histopathological subtypes. Gross total resection (Simpson I and II) was achieved in 94.5% of cases and subtotal resection (Simpson III or more) in 5.5%. The tumor recurrence rate was 4.4%, and the mortality rate related to surgery or disease progression was 3%.
Conclusion. – WHO grade I predominance was observed among spinal meningiomas, analogous to intracranial meningiomas. SMs predominated in the thoracic spine. Surgery with gross total resection was achieved in the vast majority of cases, resulting in low recurrence and mortality rates.

1. Introduction

Spinal meningiomas (SM) are lesions with favorable prognosis from the oncology and surgery perspective [1]. SM make up 25% to 46% of all spine tumors [2]. Typically, they are located in the intradural extramedullary space and grow slowly, spreading laterally into the subarachnoid space [3] and stretching the surrounding arachnoid, sometimes incorporating it but rarely the pia [4]. Clinical symptoms start when the spinal cord is compressed [3].

They are typically solitary, well-delimited and non-invasive [5] and generally do not seed other parts of the central nervous system (CNS) or body [6].

In general, the clinical manifestations are slowly progressive and widely variable, involving weakness, sensory disturbance and radicular pain [7]. In advanced stages of spinal cord compression, eccentric tumor growth leads predominantly to disassociated long tract signs or Brown-Séquard syndrome. This heterogeneity of symptoms and signs may lead to difficulties in making a timely diagnosis [7].

The literature includes a few reports describing postoperative outcomes of spinal meningiomas [7–9]. The pathogenesis, natural history, management and behavior of intracranial meningiomas have been studied extensively; however, similar information about SM remains limited. The aim of this study was to review the data published on this subject in order to create a more comprehensive natural history of SM.

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https://doi.org/10.1016/j.neuchi.2019.09.027
0028-3770/

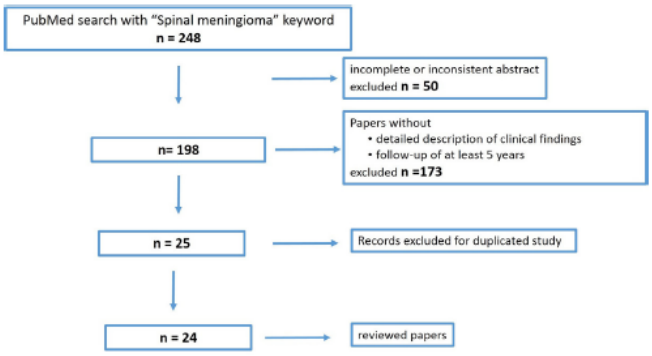

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study flow diagram.

2. Method

A review of SM-related publications was conducted through a Medline search of the literature published up to December 2018. The following inclusion and exclusion criteria were adopted for the selection steps: studies about SM were included, while papers lacking detailed descriptions of clinical findings, neuroimaging confirmation of tumor location, minimum follow-up of 5 years, and clear description of clinical findings were excluded [see Fig. 1 for the PRISMA study flow diagram].

The retreatment interval was defined as the time between the first surgery and the first subsequent treatment (either radiation therapy or a new surgical procedure). This concept was employed to avoid subjectively differentiating tumor remains from scars located near the resection sites. The extent of surgical resection was defined according to the Simpson classification [10]: gross total resection (GTR) (grades I and II) and subtotal resection (STR) (grades III, IV and V). The term "mortality rate" is related to perioperative mortality (by convention 30 days), whereas overall survival rate is related to long-term outcomes [11].

3. Results

The systematic review applying the keyword "spinal meningioma" returned 248 articles, of which 223 were excluded because of an incomplete/inconsistent abstract or an incomplete description of the clinical findings and insufficient follow-up time. Additionally, one study was excluded as it was a duplicate, resulting in 24 manuscripts being analyzed for this review (Fig. 1). In total, the data from 1829 SMs in 1811 patients were analyzed, with 1450 females and 361 males having a mean age of 57.6 years. The SMs were located in the thoracic spine (1181–64.6%) and the cervical spine (394–22.7%). Histopathological descriptions were available in 1415 cases (83.3%), including 1342 (94.8%) cases classified as grade I, with a predominance of the psammomatous (27.8%) and meningothelial (25.2%) subtypes. Grade II classification was assigned to 63 cases (4.4%) cases and grade III in 10 cases (0.8%). These patients had an average of 15.3 years' follow-up, with a range from 5 to 37 years. The extent of surgical resection according to the Simpson score was available in 1454 cases. Among those cases, GTR (Simpson I and II) was achieved in 1374 cases (94.5%) and STR (Simpson III or more) was reported in 80 cases (5.5%). Tumor recurrence was found in 75 out of 1722 cases (4.3%) where information about this parameter was provided. Only 53 deaths (3%) were recorded out of 1729 cases in which this information was provided (Table 1).

4. Discussion

This systematic review of SMs confirms that they occur most frequently in the thoracic region [9,12] and that the outcome of surgical excision is excellent, even for patients with a poor preoperative neurological status [3]. Spinal meningiomas most commonly affect middle-aged women, with a greater disparity of women to men than is seen with intracranial meningiomas. In one study, the female: male ratio was as high as 4: 1 [3]). This preponderance in women is thought to arise from a tissue response to sex hormones and subsequent growth [9]. Although the effect of sex hormones on meningiomas is suspected, several other receptor types may play a role in pathogenesis, including steroid receptors, peptidergic receptors, growth factor receptors and aminergic receptors [13].

The optimal surgical approach to SMs depends on the tumor's location and extension. One- or two-level laminectomy or hemilaminectomy is adequate for most dorsal and dorsolateral tumors, but more lateral exposure is required for tumors located ventrolateral or ventral to the spinal cord. A costotransversectomy or partial vertebrectomy may be required to improve exposure and allow for safer tumor removal [14].

The gold standard for surgical treatment of SM is complete tumor excision since it is a predictor of a good prognosis [14,15]. However, SMs in plaque [14] and recurrent meningiomas [16] are challenging as they are difficult to excise completely due to infiltration of the spinal cord parenchyma and arachnoidal layer. Calcified meningiomas are also difficult to resect due to adhesions to the spinal cord [15,17] Poor functional outcomes have been reported after surgical excision of calcified tumors [15] and postoperative neurological deterioration has been connected to lesions with massive calcifications [18,19]. Tumor size is another parameter that determines the neurological compromise, and even small extramedullary lesions can substantially compress the spinal cord and nerve roots [20,21] due to limited spinal intradural space.

The histological SM subtypes are generally similar to those of cerebral meningiomas [22,23]. The majority of SMs fit in the World Health Organization (WHO) grade I histological classification; among them, the psammomatous subtype is the most prevalent in SMs, followed by meningothelial and transitional subtypes [5,12]. This predominance has been attributed to the embryogenic lineage of the meningeal cells covering the brainstem and spinal cord, which differs from those covering the cortical convexity [24]. Less frequently, WHO grade II clear-cell and choroid subtypes and WHO grade III anaplastic SMs have been described, which foreshadow a significant risk of local recurrence [6].

Table 1
Systematic review.

Author	Year	Co	M	F	Age	No	F	C	CT	T	TL	L	C	GI	Me	T	P	O	GII	GIII	GR	SR	R	D
Katz [1]	1981	ISR	13	31	Nr	44	12	10	0	13	0	1	10	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	0	0
Levy [2]	1982	USA	19	78	53	99	36	17	0	73	0	7	17	97	52	1	20	24	0	0	90	7	4	3
Namer [3]	1987	TUR	7	22	36	30	12	10	0	20	0	0	10	29	16	0	4	9	0	0	Nr	Nr	0	1
Solero [4]	1989	ITA	31	143	57	174	29	26	0	144	0	4	26	173	52	17	99	5	0	1	168	4	9	31
King [5]	1998	UK	12	66	62.5	78	20	11	0	65	0	2	11	78	18	29	22	9	0	0	77	1	1	1
Klekamp [6]	1999	GER	24	93	57	130	13	35	0	87	0	8	35	Nr	Nr	Nr	Nr	Nr	Nr	Nr	115	15	18	6
Gezen [7]	2000	TUR	9	27	49	36	15	5	2	22	4	5	5	36	10	7	19	0	0	0	30	6	2	1
Gottfried [8]	2003	USA	5	20	60	25	12	4	0	19	0	2	4	Nr	Nr	Nr	Nr	Nr	Nr	Nr	25	0	1	0
Morandi [9]	2004	FRA	5	25	77.1	30	15	2	0	28	0	0	2	27	4	7	15	1	3	0	27	3	0	6
Schaller [10]	2005	GER	3	30	63	33	15	10	0	23	0	0	10	33	4	0	22	7	0	0	28	5	0	0
Sandalcioglu [11]	2008	GER	17	114	69	131	16	21	7	95	6	2	21	Nr	Nr	Nr	Nr	Nr	Nr	Nr	127	4	4	1
Iacoangeli [12]	2012	ITA	10	20	74.6	30	5	4	0	26	0	0	4	30	20	0	8	2	0	0	28	2	0	0
Qiang [13]	2012	CHN	8	2	13.2	10	8	5	2	3	0	0	5	8	1	0	3	4	2	0	8	2	7	1
Arima [14]	2014	JAP	8	15	60.3	23	7	14	0	9	0	0	14	Nr	Nr	Nr	Nr	Nr	Nr	Nr	18	5	Nr	Nr
Kim [15]	2015	SKO	5	15	59	20	14	8	0	12	0	0	8	20	11	4	0	5	0	0	20	0	1	0
Sun [16]	2015	USA	2	16	50	20	15	7	0	11	2	0	7	0	0	0	0	0	20	0	16	4	2	0
Tola [17]	2016	ITA	6	14	61	20	10	3	0	16	0	1	3	20	7	0	12	1	0	0	19	1	0	0
Maiti [18]	2016	USA	7	31	56	38	15	10	4	24	0	0	10	35	Nr	Nr	Nr	Nr	3	0	37	1	4	0
Ruggeri [19]	2017	ITA	3	34	62	37	13	7	0	31	0	2	7	40	Nr	Nr	29	Nr	0	0	37	3	0	0
Frati [20]	2017	ITA	35	138	55.6	173	37	25	27	119	2	0	25	170	Nr	Nr	Nr	Nr	2	1	171	2	4	0
Bayoumi [21]	2017	TUR	13	48	60.5	61	11	9	5	40	5	2	9	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
Noh [22]	2018	KSA	3	14	63.1	17	23	4	0	12	0	1	4	0	0	0	0	0	17	0	15	2	3	0
Hua [23]	2018	CHN	99	384	53.7	483	10	146	56	232	44	5	146	461	128	38	95	200	14	8	187	7	9	0
Gilard [24]	2018	FRA	17	70	64.6	87	7	22	0	57	0	8	22	85	34	8	26	17	2	0	81	6	6	2
Total			361	1450	57.6	1829	16	415	103	1181	63	50	415	1342	357	111	374	284	63	10	1324	80	75	53

Co: country (ISR: Israel; USA: United States of America; TUR: Turkey; UK: United Kingdom; GER: Germany; FRA: France; ITA: Italy; CHN: China; JAP: Japan; SKO: South Korea); M: male; F: female; Age: in years; No: Number of tumors; F: Follow-up (in years); C: cervical; CT: cervicothoracic; T: thoracic; TL: thoracolumbar; L: lumbar; GI: meningioma grade I; GII: meningioma grade II; GIII: meningioma grade III; P: psamomatous subtype; T: transitional subtype; Me: meningothelial subtype; O: other subtype; GR: gross total resection; SR: subtotal resection; R: Recurrence; D: Death; Nr: no reported.

The SM recurrence rate is low (4.3%), similar to the rate for ventricular meningiomas [25]. SM recurrence has been predicted to range from 1.3% to 6.4% and to occur within 1 to 17 years [3]. Partial resection has been implicated as a cofactor in recurrence [12], but subtotal removal does not necessarily lead to recurrence [26]. Atypical or anaplastic SM subtypes have been associated with increased recurrence [6,9,15]. Surgical management for recurrent SMs is more challenging due to the presence of arachnoid scarring, which makes radical resection difficult and increases tumor recurrence.

The mortality rate (3%) in this systematic review was low. Postoperative morbidity and mortality have progressively declined with the advent of sophisticated neuroimaging modalities, neuroanesthetic and microsurgical techniques, intraoperative ultrasonography, surgical microscopes, ultrasonic surgical aspirators, angiography, preoperative intravascular embolization and spinal cord monitoring [3,5,27]. The primary causes of death during the postoperative period [14] in the reviewed studies were pulmonary embolism, aspiration pneumonia, stroke and myocardial infarction [26,28]. In this context, ambulation and rehabilitation efforts should be prioritized in the early postoperative period, and a tapering regime of corticosteroid therapy should be instituted [20] if such therapeutic modalities are necessary.

5. Conclusions

SMs predominate in the thoracic region, mostly as histological WHO grade I tumors. Surgery with GTR is achievable in the vast majority of cases, with a low frequency of recurrence and low mortality, confirming the SM's benign nature.

Limitations

Although this study had a large sample size, its limitations should be mentioned. Information on the recurrence-free interval was obtained based on how each author had described it in the article (radiographically or need for retreatment); the kinetics of the neurological condition after surgery or corticosteroid administration were not specified in those articles. Most of the articles do not provide details about this topic, thus contributing to bias in our analysis.

Disclosure of interest

The authors declare that they have no competing interest.

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PUBLICAÇÃO 4

Título	Multiple Intracranial Meningiomas: A Case Series and Review of the Literature		
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Revista	World Neurosurgery		
Submetido	04/09/2018	**Aceito**	14/11/2018
Citação completa	Araujo Pereira BJ, Nogueira de Almeida A, Pires de Aguiar PH, Paiva WS, Teixeira MJ, Nagahashi Marie SK. Multiple Intracranial Meningiomas: A Case Series and Review of the Literature. World neurosurgery. 2019;122:e1536-e41 doi: 10.1016/j.wneu.2018.11.097.		
Fator de Impacto	1.723		
Citações	Scopus: 4; Web of Science: 3; Google scholar: 5		

Multiple Intracranial Meningiomas: A Case Series and Review of the Literature

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OBJECTIVE: To review the published data to create a more comprehensive natural history of multiple meningiomas (MM).

METHODS: A review of MM published until now was carried out through a Medline search up to August 2018. The use of the "multiple meningiomas" keyword returned 278 articles, and the characteristics analyzed in our present cohort were searched on those publications. Articles without detailed description of clinical findings, neuroimaging confirmation of tumor multiplicity, follow-up at least of 5 years, and clear description of clinical findings were excluded. We added series to this review.

RESULTS: 293 patients with MM were analyzed: 220 women and 73 men, with a total of 932 tumors (3.1 tumors per patient). The majority of tumors were located in the convexity (653% to 74.5%). The total number of tumors treated was 429 (43.9%): 338 (78.8%) by surgical resection and 91 (21.2%) by radiotherapy. Histopathologic description was available in 303 of 429 cases, being grade I in 272 (90.3%) cases, with a predominance of the meningothelial subtype (30.7%). Tumor recurrence was described in 32 (8.07%) among 397 and only 10 deaths (3.4%) of 281 reported cases, where this characteristic was evaluated.

CONCLUSIONS: World Health Organization grade I predominance was observed among multiple meningiomas in similarity to single meningiomas. Only a fraction of MM patients (43.89%) needed treatment. A benign tumor behavior was corroborated by the observed low frequency of recurrence and mortality.

INTRODUCTION

Meningiomas, which arise from arachnoidal cap cells of the leptomeninges, have an annual incidence rate of 5.5 per 100,000.[1,2] They are among the most common intracranial primary tumors, typically presenting as slow-growing sporadic solitary lesions.[3] Multiple meningiomas (MM), defined as the presence of ≥ 2 spatially separated synchronous or metachronous lesions, occur in $<10\%$ of patients with diagnoses of meningioma.[4,5] The widespread use of neuroimaging has led to a corresponding increase in the reported incidence of meningiomas.[6] The typically slow growth rate of meningiomas[7,8] and the tendency of most meningiomas to remain asymptomatic over the life course accounts for the fact that 50% of all meningiomas are discovered at autopsy.[9] Consequently, greater numbers of asymptomatic tumors are diagnosed through neuroimaging.

MM may be associated with an NF2 alteration; in such cases, the tumor develops as a consequence of a predisposing NF2 germline mutation. Furthermore, the analysis of NF2 gene mutations can potentially contribute to determining the pathogenic mechanism(s) of MM. Non-NF2-associated MM may occur as sporadic or familial cases[10] or as the result of the noncontiguous spread of a single sporadic tumor.[11] Although the physiopathologic mechanism of MM is not yet well known, 2 hypotheses have been discussed in the literature. The first suggests that these tumors occur independently, based on the histologic and cytogenetic differences observed among the different meningiomatous nodules in a single patient.[12-15] By contrast, the second hypothesis proposes a single clonal transformation, with subsequent propagation of these tumor cells through the cerebrospinal fluid constituting multiple monoclonal meningiomas. Molecular genetic analyses of meningiomatous nodules and the detection of common NF2 gene mutation have provided evidentiary support for the monoclonal origin espoused by the second hypothesis.[13,15-18]

Key words
- Multiple meningioma
- Recurrence
- Surgery

Abbreviations and Acronyms
CS: Cowden syndrome
MM: Multiple meningioma
NF2: Neurofibromatosis type 2
WHO: World Health Organization

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Citation: World Neurosurg. (2018). https://doi.org/10.1016/j.wneu.2018.11.097

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

1878-8750/$ - see front matter

An increased risk of meningiomas has been associated with tumor-susceptibility syndromes such as neurofibromatosis type 2 (NF2), Cowden syndrome (CS), and Werner syndrome, which are caused by mutations in *NF2*, *PTEN* and *RECQL2*, *PTEN*, *SDHB*, *SDHC*, *SDHD*, and *KLLN*.[19] Also, a germline *SMARCB1* mutation, causing predisposition to schwannomatosis and rhabdoid tumors, was recently identified in a family affected by multiple cranial and spinal meningiomas and schwannomas.[10] The pathogenesis, natural history, and management of solitary meningiomas have been the subject of extensive study; however, analogous knowledge about MM remains limited.[20] The aim of this study was to review the published data on the subject to create a more comprehensive natural history of MM.

METHODS

A cross-sectional study of patients with meningioma diagnoses in our institution, between 2000 and 2014, was conducted.[21] The clinical, neuroimaging, surgical, and histopathologic characteristics of patients with MM in this series were analyzed. Specifically, the characteristics analyzed in those patients included age, gender, familial history, associated malignancies, number of meningiomas, tumor sites, number of resected tumors, histopathologic classification (including tumor grade), complementary therapy, follow-up interval, tumor recurrence, and mortality. These data were retrieved from the hospital database system, which keeps records of all patients, along with dates related to medical appointments, surgical procedures, radiotherapy sessions, emergency room admissions, and in-hospital deaths. Otherwise, clinical data (Karnofsky Performance Scale, neurologic status, and medicines in use) and information about out-of-hospital death were obtained through attendance or phone interviews. This study was approved by our institutional review board under registration CAPPESq # 200/05.

For classification of tumor sites, meningiomas were grouped into 3 areas, as follows: 1) convexity (including the falcotentorial region), 2) skull base (cranial base, petroclival, and cerebellopontine angle), and 3) intraventricular. The convexity area was defined, for this study, as the dura mater of the calvarium, and the falcotentorial area was defined as the region comprising the falx, tentorium, and the calvarium areas, containing the sagittal, transverse, or sigmoid sinus. The skull base was defined as the surrounding area of the carotid artery and cranial nerves, from I to VI. The petroclival area was defined as the region in the posterior fossa surrounding the petrous bone or the lower segment of the clivus, which are the regions related to cranial nerves, from VII to XII, and the vertebral artery, along with the cerebellopontine angle cisternas, which consists of the triangular subarachnoid space between the anterior surface of the cerebellum and the lateral surface of the pons, containing cranial nerves VII and VIII and the anterior inferior cerebellar artery.[22]

The retreatment interval was delineated as the time between the first surgery and the first subsequent treatment (either radiotherapy or a new surgical procedure). This concept was used to avoid subjectively differentiating tumor remains from scars near the resection sites.

Aiming to compare this dataset from the MM from our institution, we conducted a review of the MM-related material published to date in the literature by performing a Medline search up to August 2018. The use of the keyword "multiple meningiomas" returned results consisting of 278 articles; the characteristics analyzed in our present cohort were searched within those publications. As a first selection step, we adopted the following inclusion and exclusion criteria: 1) series reports about MM were included, whereas 2) articles lacking detailed descriptions of clinical findings, neuroimaging confirmation of tumor multiplicity, follow-up periods of at least 5 years, and clear descriptions of clinical findings were excluded (Figure 1).

RESULTS

Among the 629 patients with meningiomas previously analyzed in our cohort,[21] 21 patients (3.3%) (16F:5M) presented with MM. Thirty-nine of 58 diagnosed tumors (ranging from 2 to 7 meningiomas per patient) were resected, and patients' ages ranged from 31 to 82 years (average, 55.8 ± 11.26 years). Twenty patients presented with grade I meningioma and only 1 patient with a grade II meningioma, pursuant to the 2007 World Health Organization (WHO) meningioma-grading criteria.[23] Four patients (19%) presented with other associated tumors, as follows: thyroid (2 cases), breast (1 case), and gastrointestinal tract (1 case), and they met the criteria for CS based on their medical records.

The above findings were compared with the results identified in a literature review conducted after the selection flow presented in Figure 1, which yielded 9 articles about MM, reported from worldwide centers and satisfying the adopted criteria, up to August 2018. We added our 21 patients presenting with MM into this comparative analysis (Table 1). In total, the data from 293 patients with MM were analyzed. These patients included 220 women and 73 men, with a mean age of 53.7 ± 8.3 years. These patients presented with a total of 932 tumors (3.1 tumors per patient) A majority of patients' tumors were located in the convexity (653% to 74.5%), followed by skull base (220% to 25.1%), and ventricular (45 to 0.4%). The total number of tumors treated was 429 (43.9%): 338 (78.8%) by surgical resection and 91 (21.2%) by radiotherapy. Histopathologic description was available in 303 of 429 cases, being grade I in 272 (90.3%) cases, with a predominance of the meningothelial subtype (30.7%). Grade II classification was attributed to 26 (8.1%) cases and grade III to 5 (1.6%) cases. These patients received follow-up care for an average of 21.4 ± 8.6 years (range, 11 to 35 years). Tumor recurrence was cited in 32 (8.07%) of 397 cases for which the information about this characteristic was available. Only 10 deaths (3.4%) were recorded, out of 281 reported cases, in cases that allowed evaluation of this characteristic was evaluated (Table 1).

DISCUSSION

The term "multiple meningioma" (MM) was coined by Cushing and Eisehardt[11] to describe the occurrence of multiple tumors in the absence of neurofibromatosis or acoustic neuromas. The term is applicable when at least 2 spatially separated meningiomas present at once or when more than 2 meningiomas manifest sequentially from 2 clearly distinct regions.[30]

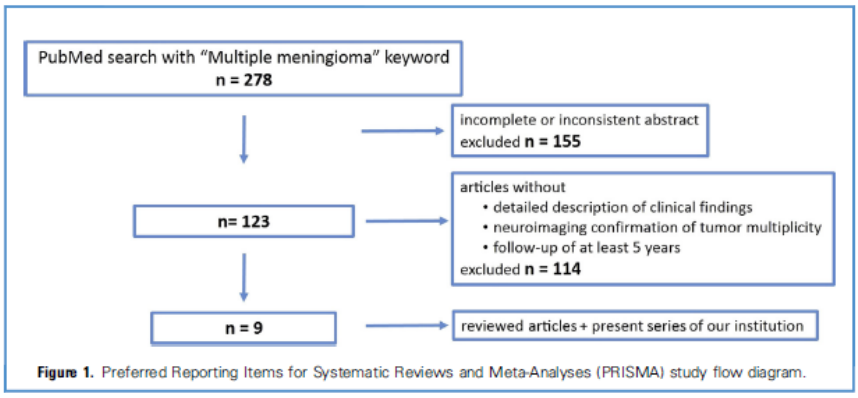

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram.

MMs are more common in women, and this female predilection is significantly higher (3.5:1) than any observed for cases of single meningiomas,[24,25,27] in which the gender ratio varies but is approximately 2F:1M.[31-33] The reason for such an unbalanced gender distribution remains unclear; however, higher progesterone expression identified in these MMs than in single meningiomas may account for the preponderance of women in MM cases.[27,34] These MMs are rarely found in childhood and adolescence.[24,35]

No difference in the WHO grade distribution of MMs relative to single meningiomas has been observed, and grade I tumors are preponderant in both,[24] with a predominance of the meningothelial subtype.[25] Interestingly, MMs tend to be spatially distributed, demonstrating a predominance in convexity, which may corroborate the hypothesis related to subarachnoid tumor cell dissemination as the origin of MMs. Further corroborating this hypothesis is that MMs have been identified more frequently at 1 hemicranial space,[11,12] but they may be bilateral.[11,36] Radiation-induced meningiomas are located exclusively at the site of x-ray exposure, and when the irradiation is used to treat tinea capitis, associated meningiomas present in calvaria.[37] MMs in posterior fossa are rare.[38]

Larson et al.[17] and von Deimling et al.[18] have reported that MMs might arise from a single progenitor cell and could then spread throughout the subarachnoid space. However, others claim that MMs originate from multiple foci and are not the result of cell migration through the subarachnoid space.[12,14,39]

The molecular alterations in MMs differ, depending on whether they are sporadic, radiation-induced, or familial cases.[17,40,41] MMs are associated with the presence of other types of solid tumors in several familial syndromes, such as NF2, nevoid basal cell carcinoma syndrome, CS, and Werner syndrome.[19] In CS, germline mutations have been described in a subset of the established susceptibility genes, as phosphatase and tensin homolog (*PTEN*), succinate dehydrogenase B-D (SDHB, SDHC, SDHD), and killin (*KLLN*),[42] and a 45-fold increased risk for epithelial thyroid cancer in these patients has been reported, relative to the risk in the general population of the United States.[43] CS is estimated to affect between 1 in 200,000 to 250,000 people.[44,45] Although the presence of meningioma is not included in the diagnostic criteria of this syndrome, this type of tumor is found in approximately 8% of patients.[46] The PTEN hamartoma tumor syndrome is an autosomal dominant disorder described in CS, and it is caused by germline mutations in *PTEN*.[47,48] CS patients harboring no germline PTEN mutations were found to have germline mutations in *SDH B/C/D* or others present *KLLN* promoter hypermethylation.[42,49] Succinate dehydrogenase is part of the mitochondrial complex II that participates in both the electron transport chain and the Krebs cycle,[50] whereas killin is a p53-regulated DNA replication inhibitor.

CS has also been associated with heterozygous mutations in *AKT1* and *PI3KCA*[51] and with missense mutation in *SEC23B*,[52] a component of COPII vesicles for anterograde ER-to-Golgi transport.[53,54] *SEC23B* variants have been detected in sporadic breast, thyroid, and endometrial cancers, and it has been suggested that these variants play functional roles in sporadic thyroid carcinogenesis.[52]

The therapeutic approach to treating MMs includes surgery, whole-brain radiation, and stereotactic radiosurgery, despite conflicting data in the literature.[55] Overall benefits and risks should be considered in the selection of treatment, as, for example, the acute, subacute, and delayed effects of radiation in a young and active patient.[56] Surgery remains the treatment of choice and should be indicated for symptomatic meningiomas >3 cm with surgical accessibility, faster growth, or the presence of peritumoral edema.[8,24,36] However, the benefits of aggressive surgical procedures to reduce recurrence have been subject to debate in the literature,[57] inasmuch as the majority of the analyzed tumors, including those within our study, were small and asymptomatic. These tumors are also slow growing, as calculated by Wong et al.,[29] with an average growth rate of 0.46 cm^3/year, according to a retrospective analysis of 55 tumors in 12 patients. Moreover, no significant relationship between the number of meningiomas and growth rates has been observed.[58] The prognosis for patients with MMs is good and does not differ meaningfully from that of solitary meningiomas, except in cases of radiation-induced MM and meningiomas associated with NF2 in children.[25,36]

Table 1. Systematic Review of Studies of Multiple Meningiomas

Study	Country	M	F	Age	N	Follow-Up, years	C	SB	V	Treatment	GI	ME	T	F	Ot	GII	GIII	RT	CM	Rec	D
Sheehy and Crockhard, 1983[24]	UK	0	10	51.4 ± 14.4	36	34	28	8	0	nr	10	0	0	2	7	0	0	0	0	0	0
Butti et al., 1989[12]	Italy	4	4	53.2 ± 9.1	23	13	20	3	0	23 (100%)	23	15	7	0	1	0	0	0	0	3	0
Domenicucci et al., 1989[25]	Italy	13	1	50.3 ± 9.6	33	35	28	5	0	31 (93.9%)	31	0	0	14	17	0	0	0	2	0	0
Turgut et al., 1997[11]	Turkey	1	5	30.7	23	8	21	2	0	23 (100%)	23	0	5	3	15	0	0	0	0	0	1
Salvatti et al., 2004[26]	Italy	10	25	52.4	152	20	106	46	0	87 (56.1%)	33	13	6	9	5	3	2	0	0	0	1
Huang et al., 2005[27]	Germany	4	35	57.9	95	11	63	32	0	59 (62.1%)	55	29	12	9	5	4	0	0	0	11	6
Birckhead et al., 2012[28]	USA	6	9	24.0	62	21	43	15	4	59 (53.1%)*	2	nr	nr	nr	nr	2	nr	15	0	4	1
Wong et al., 2013[29]	USA	1	11	37.0	55	20	nr	nr	nr	32 (58.1%)*	nr	nr	nr	nr	nr	nr	nr	4	1	nr	Nr
Tsermoulas et al., 2017[20]	Canada	29	104	58.0	395	25	294	101	0	87 (22%)	68	nr	nr	nr	nr	16	3	27	48	11	0
Pereira et al., 2018 (present study)	Brazil	5	16	54.9 ± 13	58	14	50	8	0	28 (48.27%)	27	5	8	1	13	1	0	0	0	3	1
Total		73	220	53.7 ± 8.3	932		653	220	4	429 (43.89%)	272	62	38	38	64	26	5	46	51	32	10

C, convexity; SB, skull base; V, ventricle; GI, meningioma grade I; T, transitional subtype; F, fibrous subtype; Me, meningothelial subtype; Ot, others subtype; GII, meningioma grade II; GIII, meningioma grade III; RT, radiotherapy after initial treatment; CM, conservative management; Rec, recurrence; D, death; nr, not reported.
*Tumors treated by radiotherapy.

Low rates of morbidity and mortality have been reported for MMs. The recurrence rate was estimated at 19% for intracranial meningiomas over 20 years, with doubling times ranging from 138 to 1045 days,[58] and several studies have shown any increment of this recurrence rate for MMs.[11,25,59]

No specific recommendation was reported for a specific method of follow-up to MMs; however, the possibility of late-onset meningiomatous nodules demands sustained long-term monitoring. The frequency of radiologic examinations for the surveillance of small, asymptomatic, and cerebral edema–free meningiomas will be adapted according to the growth rate of the various tumors, as determined by volumetric analysis.[35]

Limitations

Although this study had a large sample size, its limitations should be mentioned. Information on the recurrence-free interval, obtained after the description of the article, as defined by each author (radiographically or need for retreatment), was not specified in those articles. Most articles did not present the details of this topic, which constituted a major factor impeding this analysis.

CONCLUSIONS

WHO grade I predominance was observed among multiple meningiomas, analogously to single meningiomas. MMs predominate in the brain convexity, corroborating a subarachnoid tumor–seeding hypothesis to account for the origin of these tumors. Surgery, either at the time of initial tumor detection or during tumor surveillance, was the chosen therapeutic modality for the majority (78.8%) of reviewed MM cases, and only 21.2% of MM patients underwent radiation therapy. However, it is worth noting that only a fraction of MM patients (43.89%) even required treatment, given that the majority of the tumors were small and asymptomatic. A benign tumor behavior was demonstrated by the low frequency of recurrence and the low mortality observed in the present review of MM cases.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 4 September 2018; accepted 12 November 2018

Citation: World Neurosurg. (2018). https://doi.org/10.1016/j.wneu.2018.11.097

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

PUBLICAÇÃO 5

Título	Assessment of hemorrhagic onset on meningiomas: Systematic Review		
Autores	Benedito Jamilson Araujo Pereira, Antonio Nogueira de Almeida, Wellingson Silva Paiva, Paulo Henrique Pires de Aguiar, Suely Kazue Nagahashi Marie		
Revista	Clinical Neurology and Neurosurgery		
Submetido	24/06/2020	**Aceito**	20/08/2020
Citação completa	Pereira BJA, de Almeida AN, Paiva WS, De AguiarPH, Marie SKN. Assessment of hemorrhagic onset on meningiomas: Systematic Review. Clinical neurology and neurosurgery. 2020 Sep 22;199:106175. doi: 10.1016/j.clineuro.2020.106175.		
Fator de Impacto	1.672		
Citações	Scopus: 0; Web of Science: 0; Google scholar: 0		

Clinical Neurology and Neurosurgery 199 (2020) 106175

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Assessment of hemorrhagic onset on meningiomas: Systematic review

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ARTICLE INFO

Keywords:
Bleeding meningioma
Prognostic
Histopathologic

ABSTRACT

Objective: To review the data published on the subject to create a more comprehensive natural history of the haemorrhagic onset of meningiomas (IVMs).
Patients and methods: A Medline search up to June 2020, using the search term "bleeding meningioma," returned 136 papers. As a first selection step, we adopted the following inclusion criteria: series and case reports about bleeding meningioma. Papers written in other languages but with abstracts written in English were also evaluated.
Results: A total of 190 tumours were evaluated, specifically 109 tumours from female patients and 81 tumours from male patients with a ratio of 1.34 female to 1.0 male (mean age of 54.86 ± 16.1years old). The majority were located in the convexity (129–67.9 %). Among the 190 tumours evaluated, 171 patients (90 %) presented with GI tumours, with a predominance of the meningothelial subtype (32.6 %). Nine patients (4.7 %) presented with grade GII tumours, and 10 (5.3 %) presented with GIII tumours. The most prevalent type was intracerebral haemorrhage (ICH) at 50 %, followed by subdural at 27.36 %; the mortality rate was 13.1 % (25 deaths), the distribution of both location (prevalence of convexity: 18–72 %) and histopathology (grade 1: 22–88 %).
Conclusion: These tumours follow the histopathological distribution of meningiomas, in general. The age distribution shows prevalence among the adult population but with a greater proportion in the elderly. The fact that the overwhelming majority of cases involve meningiomas with a benign histological subtype is noteworthy. Another relevant factor observed is that most reports are from Asian origin.

1. Introduction

According to previously reported cases, the reported incidence of spontaneous meningioma haemorrhage ranges from approximately 0.5%–2.4%. [1,2]. Although meningiomas encompass a broad spectrum of symptoms and signs, their acute presentation with a haemorrhagic onset appears to be a rare event [1,3]. The rarity of this condition not only makes determining causative factors of the haemorrhage challenging, but it also makes the mechanisms of spontaneous haemorrhage harder to understand [1,4]. Some reports have suggested a positive correlation between the intratumoral vasculature and meningioma haemorrhage [5–7], but other studies have found no significant correlation [3,8].

Spontaneous haemorrhage in meningioma is uncommon and not related to sex, age, blood dyscrasia, hypertension, or tumour location [2, 9–12]. Hell and Conley reported a relatively high risk of bleeding in angioblastic and malignant meningioma [13]. However, the majority of meningiomas manifesting haemorrhage are benign variants.

Considering the rarity of meningioma bleedings, we compiled all the results of the reported series and case reports in the literature to form a more comprehensive natural history of these tumours.

2. Methods

A Medline search up to June 2020 using the key phrase "meningioma bleeding" returned 136 papers; we based our revision on this initial corpus. As a first selection step, we adopted the following inclusion criteria: series and case reports about the issue written in English, as well as papers written in other languages but with abstracts written in English; we excluded papers in which the authors did not report histological subtype or demographic data. One hundred and thirty six papers fulfilled the above criteria (see Fig. 1 for the PRISMA study flow

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https://doi.org/10.1016/j.clineuro.2020.106175
Received 24 June 2020; Received in revised form 1 August 2020; Accepted 20 August 2020
Available online 22 September 2020

diagram). These papers gathered data from 190 patients, on whom the present analysis of meningioma bleeding and neuro-oncological management was based.

According to the World Health Organization (WHO), the age groups of the population are defined as follows: young people are under the age of 15, adults are those aged 15–64, and the elderly are those over the age of 65 [14].

3. Results

A total of 190 tumours were evaluated (109 from female patients and 81 from male patients; 1.34 female/1.0 male ratio), and the majority were located in the convexity (129–67.9 %). Among the 190 tumours evaluated, 171 patients (90 %) presented with GI tumours, with a predominance of the meningothelial subtype (32.6 %). Nine patients (4.7 %) presented with grade GII tumours, and 10 (5.3 %) presented with GIII tumours.

These data were the result of a 136 manuscripts from worldwide centres, up to June 2020, that were selected for the present analysis. We analysed studies from all continents (see Table 1 and Fig. 2).

3.1. Age

The confirmed ages of the included patients at diagnosis ranged from 4 months to 85 years (mean age of 54.86 ± 16.1 years old). The histopathological distribution and mortality rates related to each age group are listed in Table 2.

3.2. Type of bleeding

In our review, we separated the types of bleeding into 3 categories: subarachoideal haemorrhage (SAH), subdural haematoma, intracerebral haematoma (ICH), and intrapulmonary haemorrhage (IPH). The most prevalent type was ICH (50 %), followed by subdural (27.36 %) and SAH (21.57 %); IPH presentation is rare (1%). It is worth mentioning that in 6 cases (3.15 %), haemorrhage was related to an interventionist procedure to embolize meningioma.

3.3. Mortality

Among the cases reported in the literature, 190 presented reports of a disease, and, in total, we observed 25 deaths (13.1 %). Among the deaths, we saw an average age of 60.12 ± 16 years old; there was no gender interference (13 female and 12 male); the distribution of both location (prevalence of convexity: 18–72 %) and histopathology (grade 1: 22–88 %) obeyed the distribution of cases in general.

4. Discussion

Meningiomas are the most commonly encountered benign intracranial lesion, accounting for roughly one quarter of all primary intracranial lesions. While the incidence of haemorrhage into brain tumours is noted to be close to 4%—mostly in gliomas and metastatic tumours—the incidence in meningiomas is much lower, roughly 1.3 % [6,15,16]. haemorrhage arising from a meningioma can manifest in several ways, including subarachnoid haemorrhage (commonly seen with parasagittal and falcine meningioma [1]), intracerebral, and, least commonly, intratumoral haemorrhage [6]. Rarely, subdural hematoma, (usually associated with convexity location) may also be seen [15]. This review demonstrates a different point, i.e., that although other previous papers have shown that subdural hematoma is rare, they proved to be the second most prevalent type of bleeding (27.36 %).

The mechanisms of intratumoral bleeding are still controversial and include the rupture of tumour blood vessels, tumour necrosis, and the invasion of brain parenchyma. Capillary growth in brain tumours has been classified into three groups: axial, retiform, and glomeruloid. It has been reported that most tumours contain a combination of these capillary types, but only the retiform type is associated with significant intratumoral haemorrhage [17]. Still, many other mechanisms have been proposed, such as progressive vessel parietal weakening due to variation in tumoral stromal support, vessel disruption/distortion by the tumour, venous hypertension, endothelial proliferation with secondary vascular occlusion, formation of abnormal blood vessel, even in not atypical or malignant meningiomas, stretching of bridging veins by the tumour with subsequent rupture with or without trauma, intratumoral vaso-active substance release (e.g., histamine), and direct meningioma fragmentation with bleeding [18]. Apparent discrepancy may be explained, in part, by the fact that the tumour vasculature is heterogeneous and different studies have not applied the same vascular marker. Varying characteristics of blood vessels have been identified in prostate cancer, lung cancer, and renal cell carcinoma through various vascular markers [19–21]. For example, 2 distinct types of blood vessels have been identified in renal cell carcinoma: undifferentiated (CD31þ/ CD34) and differentiated (CD31þ/CD34þ) vessels. Most importantly, only the undifferentiated vessels had a significant correlation with higher tumour grades [21]. The exact etiopathogenesis of bleed in our case is difficult to explain as the lesion proved to be a Grade 1 meningothelial meningioma on histopathology, and such presentation is very rare in the pathology mentioned above. The most likely cause for the ITH in our case may be attributed to the ill-formed new blood vessels which bled or the vascular erosion caused by the tumor [22].

Another possibility would be that, according to the growth of the tumour, the possibility of intratumoral infarction with subsequent haemorrhage changes. This might be an important event in the process of peritumoural haemorrhage. There may also be underlying causes, such as thrombosis, oedema, vessel erosion, and rapid tumour growth that eventually result in infarction. Some stressful conditions, such as seizure and a rapid change in blood pressure, may also act as contributing factors, such as thrombosis of the intratumoural vessels, extensive tumour infarction, and peritumoural vessel dilatation. One could insist that intratumoural infarction is not the cause of haemorrhage, but the result. However, extensive infarction of the tumour does not usually occur in cases of peritumoural haematoma, and the peritumoural dilatation of vessels cannot be explained [6]. Wang et al. [23] explore the characteristics of tumor vessels, the pericyte coverage of blood vessels was evaluated by staining for the pericyte marker SMA. The results

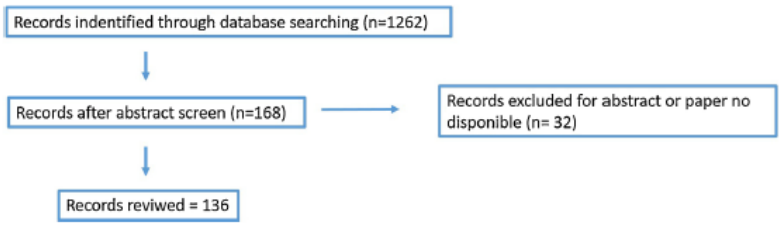

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study flow diagram.

Table 1
Literature Review.

					Gender		Location						GI Subtype									
Author	Year	Country	Age	Bleeding	M	F	Con	SB	V	Sp	Lu	GI	*F*	*T*	*M*	*P*	*A*	*Orh*	GII	GIII	GTR	Dt
Gardner*[1]	1931	nr	18	ICH	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	nr	nr
Cushing*[1]	1938	USA	27	SAH	1	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	nr	nr
			53	SAH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	nr	nr
Huang[2]	1954	Japan	27	SAH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Moore[3]	1954	USA	72	SAH	0	1	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	1
			66	SAH	1	0	1	0	0	0	0	1	0	0	0	0	1	0	0	0	0	1
Askenazy[4]	1960	Israel	34	SAH	0	1	0	0	1	0	0	1	0	0	0	1	0	0	0	0	1	1
			38	SAH	0	1	0	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0
			32	SAH	1	0	0	0	1	0	0	1	0	0	0	1	0	0	0	0	1	0
El Banhawy[5]	1962	nr	15	SAH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
			72	SAH	1	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1	0
			20	SAH	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Taptas[6]	1961	Greece	0.3	Subdural	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Goran[7]	1965	USA	65	ICH	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0
			68	SAH	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	1
			46	ICH	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1
			55	ICH	1	0	0	0	1	0	0	1	0	0	1	0	0	0	0	0	1	0
			42	ICH	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1
Bilodeau[8]	1966	Canada	46	ICH	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	1
Bingas*[1]	1966	nr	65	Subdural	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Skultety	1968	USA	58	SAH	1	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Gruszkiewicz[9]	1969	Israel	18	ICH	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Cusick[10]	1972	USA	47	Subdural	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1
Hung[11]	1972	China	42	ICH	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Fukumitsu*[1]	1973	Japan	49	ICH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	nr	nr
Rosenberg[12]	1975	USA	44	SAH	1	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0	1	0
			48	SAH	0	1	0	1	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Shinmura[13]	1976	Japan	43	SAH	0	1	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
Modesti[14]	1976	USA	59	Subdural	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
			49	ICH	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0
			72	Subdural	0	1	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	1
			69	ICH	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0
Yasargil[15]	1976	SWZ	50	SAH	0	1	0	1	0	0	0	1	0	0	0	1	0	0	0	0	1	0
Fortuna*[1]	1977	nr	49	SAH	0	1	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Budny[16]	1977	USA	60	ICH	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Bruno*[1]	1979	Nr	78	ICH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	0	1
Ohaegbulam[17]	1977	Nigeria	40	SAH	1	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Walsh[18]	1977	USA	77	Subdural	1	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1	1
Everett[19]	1979	USA	65	Subdural	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	1
Hammer[20]	1979	Germany	36	ICH	1	0	0	1	0	0	0	1	0	0	0	0	0	1	0	0	1	0
Helle[21]	1980	USA	77	ICH	1	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Nishijama[22]	1980	Japan	21	ICH	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	1	1	0
Lazaro[23]	1981	USA	46	ICH	1	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	1	0
Latchaw[24]	1981	USA	46	SAH	0	1	0	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0
Tsuchida[25]	1981	Japan	46	ICH	1	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Toledo[26]	1981	Israel	59	Subdural	0	1	0	0	0	1	0	1	0	0	1	0	0	0	0	0	1	0
Reverdan[27]	1981	France	49	Subdural	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	nr	0
Sakai[28]	1981	Japan	36	Subdural	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Kaur[29]	1982	India	22	ICH	1	0	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
Patil[30]	1982	USA	75	Subdural	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Pluchino[31]	1983	Italy	47	SAH	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0
			46	SAH	0	1	0	1	0	0	0	1	0	0	0	0	0	1	0	0	1	0

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Table 1 (*continued*)

Author	Year	Country	Age	Bleeding	Gender		Location						GI Subtype									
					M	F	Con	SB	V	Sp	Lu	GI	F	T	M	P	A	Oth	GII	GIII	GTR	Dt
Brambilla[32]	1983	Italy	76	SAH	0	1	0	1	0	0	0	1	0	0	0	0	1	0	0	0	1	1
Kohli[33]	1984	USA	37	ICH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Baskinis[34]	1984	Greece	68	Subdural	1	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	1	0
Hosaka[35]	1985	Japan	65	ICH	1	0	0	0	1	0	0	1	0	0	0	0	1	0	0	0	1	0
Kotwica[36]	1986	Poland	32	Subdural	1	0	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
Shojima[37]	1986	Japan	76	SAH	1	0	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
Watanabe[38]	1986	Japan	63	Subdural(eb)	0	1	0	1	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Scotti[39]	1987	Italy	26	SAH	1	0	0	0	0	1	0	1	0	0	0	1	0	0	0	0	1	0
Suyama[40]	1987	Japan	37	ICH (eb)	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Hayama[41]	1987	Japan	73	SAH (eb)	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Bloomgarden[42]	1987	USA	65	SAH	0	1	0	1	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Kabuto[43]	1987	Japan	37	ICH	0	1	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
			59	ICH	0	1	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Hawkins[44]	1988	UK	31	SAH	1	0	0	0	0	1	0	1	0	0	0	0	1	0	0	0	1	0
Tokunaga[45]	1988	Japan	61	Subdural	0	1	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Jones[46]	1989	Australia	73	Subdural	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1
			58	ICH	0	1	0	1	0	0	0	1	1	0	0	0	0	0	0	0	1	0
			78	ICH	1	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	1	0
			76	Subdural	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	nr	1
Kurokawa[47]	1989	Japan	81	ICH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	nr
Russel*[1]	1989	UK	58	ICH	1	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Niwa[48]	1989	Japan	63	ICH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Sato[49]	1989	Japan	46	Subdural	0	1	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
Chang[50]	1990	India	56	Subdural	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Nikkawa[51]	1990	Japan	49	Subdural	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0
Martínez-lage[52]	1991	Spain	67	SAH	0	1	0	1	0	0	0	1	1	0	0	0	0	0	0	0	nr	nr
			70	Subdural	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	nr	nr
			50	ICH	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	1
Nakao[53]	1991	Japan	56	SAH	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0
Renowden[54]	1992	UK	41	Subdural	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0
Chaskis[55]	1992	Belgium	59	Subdural	0	1	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
			62	Subdural	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	1
Chen[56]	1992	USA	79	Subdural	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Ueno[57]	1993	Japan	67	Subdural	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Kounitchev[58]	1993	Bulgaria	26	Subdural	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Cervoni[59]	1993	Italy	58	SAH	0	1	1	0	0	0	0	0	0	1	0	0	0	0	0	1	1	0
			42	SAH	0	1	0	1	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Popovic[60]	1994	USA	47	Subdural	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Tanaka[61]	1994	Japan	47	Subdural	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Lang[62]	1995	UK	64	ICH	1	0	0	0	1	0	0	1	0	0	1	0	0	0	0	0	1	0
Yoshioka[63]	1995	Japan	76	ICH	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1
Spektor[64]	1995	Israel	73	Subdural	0	1	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
Germano[65]	1996	Italy	53	SAH	1	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	1	0
Onesti[66]	1996	USA	72	ICH	1	0	1	0	0	0	0	1	nr	nr	nr	nr	nr	nr	0	0	1	0
Mural[67]	1996	Japan	39	ICH	0	1	0	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0
Morimoto[68]	1996	Japan	67	SAH	0	1	0	0	0	1	0	1	0	0	0	1	0	0	0	0	1	0
Kallmes[69]	1997	USA	61	ICH(eb)	0	1	0	1	0	0	0	1	0	0	0	0	1	0	0	0	nr	nr
Moriyama[70]	1998	Japan	68	Subdural	1	0	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
Scarrow[71]	1998	USA	77	Subdural	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Okuno[72]	1998	Japan	78	ICH (eb)	0	1	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Wakamoto[73]	1998	Japan	56	ICH	1	0	0	1	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Shimizu[74]	1998	Japan	67	Subdural	1	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Sunada[75]	1998	Japan	48	Subdural	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Thimothy[76]	1999	UK	64	Subdural	1	0	1	0	0	0	0	1	0	1	0	0	0	0	0	1	0	0

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Table 1 (*continued*)

Author	Year	Country	Age	Bleeding	Gender		Location						GI Subtype									
					M	F	Con	SB	V	Sp	Lu	GI	F	T	M	P	A	Oth	GII	GIII	GTR	Dr
Roux-Villard[77]	1999	France	65	ICH	1	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1	0
			49	ICH	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Lieu[78]	1999	China	19	SAH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
			44	ICH	1	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
			29	ICH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Yilcesoy[79]	1999	Turkey	48	SAH	0	1	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Okuno[72]	1999	Japan	78	Subdural	0	1	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Kim[80]	2000	Korea S.	77	ICH	1	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
			72	ICH	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1
			65	ICH	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
Lee[81]	2001	Korea S.	43	ICH	0	1	0	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0
Lefranc[82]	2001	Belgium	59	Subdural	0	0	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
			62	Subdural	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
			68	Subdural	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	1
			85	Subdural	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
Rabistein[83]	2002	USA	84	Subdural	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Dallocchio[84]	2003	Italy	73	ICH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Ishimaru[85]	2003	Japan	53	ICH	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
			64	ICH	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
			82	ICH	0	1	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
			68	ICH	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	1
			68	SAH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
			68	ICH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
De Silva[86]	2004	UK	61	Subdural	0	1	0	1	0	0	0	1	0	0	1	0	0	0	0	0	nr	nr
Kim[87]	2004	Korea S.	52	ICH	0	1	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Kouyialis[88]	2004	Greece	72	ICH	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0
Yu[89]	2004	China	61	ICH (eb)	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Sakowitz[90]	2004	Germany	50	ICH	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0
Bosnjak[1]	2005	Slovenia	44	SAH	0	1	0	1	0	0	0	1	0	0	0	0	0	0	1	0	1	0
			74	ICH	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Di Rocco[91]	2006	Italy	72	Subdural	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
			74	Subdural	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Palimento[92]	2006	Italy	45	IPH	0	1	0	0	0	0	1	1	0	0	0	0	1	0	0	0	1	0
Mitushira[93]	2006	Japan	60	Subdural	0	1	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Zyial[94]	2006	Turkey	57	ICH	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0
Romeike[95]	2007	Germany	57	ICH	0	1	0	0	1	0	0	1	1	0	0	0	0	0	0	0	1	1
Rim[96]	2008	Korea S.	53	SAH	1	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Kagoshima[97]	2008	Japan	49	ICH	0	1	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Miyazawa[98]	2008	Japan	66	ICH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Kashimura[99]	2008	Japan	55	ICH	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0
Izumi[100]	2009	Japan	18	IPH	1	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	1	0
Worm[101]	2009	Brazil	64	Subdural	1	0	0	1	0	0	0	1	0	0	0	0	0	1	0	0	1	0
Mangubat[102]	2010	USA	62	ICH	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Belluf[103]	2011	SWZ	65	ICH	1	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Czyz[104]	2011	Poland	69	Subdural	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Fu[105]	2011	China	46	ICH	0	1	1	0	1	0	0	1	0	1	0	0	0	0	0	0	1	0
Yamaguchi[106]	2011	Japan	34	ICH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Motegi[107]	2012	Japan	29	ICH	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	1	1	0
Khrist[108]	2012	USA	50	ICH	1	0	0	1	0	0	0	1	0	0	0	0	0	1	0	0	1	0
Rocha[109]	2012	Brazil	52	Subdural	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	nr	nr
Viji[110]	2012	India	16	ICH	1	0	0	0	0	1	0	1	0	0	0	0	1	0	0	0	1	1
			45	ICH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Lee[111]	2013	India	22	ICH	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
Alnaami[112]	2013	Canada	34	ICH	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0

(continued on next page)

Table 1 (*continued*)

Author	Year	Country	Age	Bleeding	Gender		Location					GI	GI Subtype						GII	GIII	GTR	Dt
					M	F	Con	SB	V	Sp	Lu		*F*	*T*	*M*	*P*	*A*	*Oth*				
Gupta[113]	2013	India	30	ICH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Lee[114]	2013	S. Korea	58	ICH	0	1	0	0	0	1	0	1	1	0	0	0	0	0	0	0	1	0
Sasagawa[115]	2013	Japan	72	ICH	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0
Kanamori[116]	2013	Japan	64	SAH	0	1	0	1	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Eljebbouri[117]	2014	Morocco	51	Subdural	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Ashok[118]	2014	India	65	ICH	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
Hambra[119]	2014	Italy	59	Subdural	1	0	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
Kim[120]	2015	Korea S.	61	Subdural	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Yasuyuki[121]	2015	Japan	78	ICH	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Ayoma[122]	2015	Japan	59	SAH	0	1	0	1	0	0	0	1	0	1	0	0	0	0	0	0	1	0
Wang[123]	2016	China	39	ICH	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
			45	ICH	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
			51	ICH	0	1	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0
			53	ICH	0	1	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
			59	ICH	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
			64	ICH	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Fric[124]	2016	Norway	68	ICH	0	1	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Sinurat[125]	2017	Indonesia	46	ICH	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Nery[126]	2017	Brazil	85	ICH	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0
Prickett[127]	2018	USA	49	ICH	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Suzuki[128]	2018	Japan	61	ICH	0	1	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
Masoudi[129]	2018	Iran	36	Subdural	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0
Mandour[130]	2018	Morocco	61	ICH	1	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Gajbhye[131]	2019	India	54	ICH	0	1	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1	0
Moon[132]	2019	S.Korea	35	ICH	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	1	0
Aloraidi[133]	2019	Saudi A.	49	ICH	0	1	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0
			49	ICH	0	1	1	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0
Kim[134]	2019	USA	68	ICH	0	1	0	0	0	1	0	1	0	0	1	0	0	0	0	0	1	0
Schartz[135]	2019	USA	46	ICH	1	0	0	0	1	0	0	1	0	0	0	0	0	0	1	0	1	0
Matsuoka[136]	2019	Japan	61	ICH	0	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0

Table Legends: M: male; F: female; Con: convexity; SB: skull base; V:ventricles; Sp: spine; Lu: Lung; GI: meningioma grade I; GII: meningioma grade II; GIII: meningioma grade III; *F*: fibrous subtype; *T*: transitional subtype; *M*: meningothelial subtype; *P*: psamomatosus subtype; *A*: angiomathosus subtype; *OT*: others subtypes; GTR: gross total resection; NR: no reported; (eb): previous embolization; *: Articles cited by the Bosnjack 2005 review; mean age (years old).

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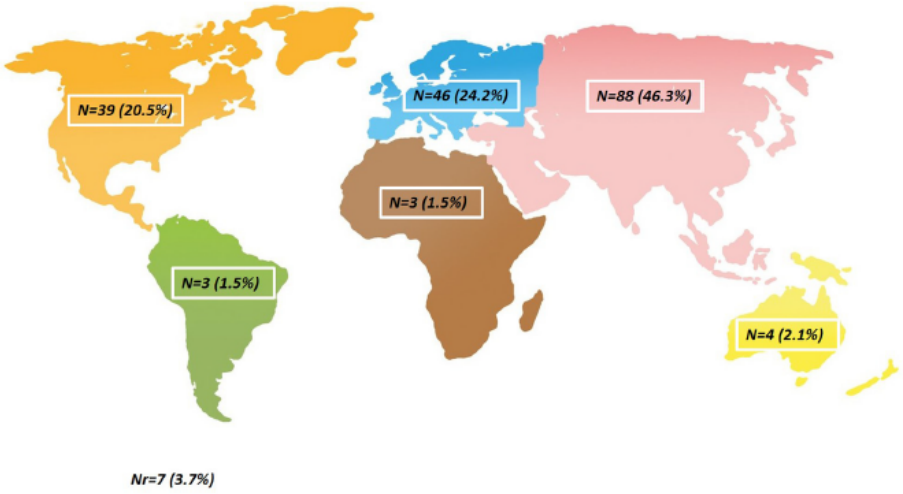

Fig. 2. Distribution of cases based on each continent.

Table 2
Distribution according age group.

	Gender		Location					GI Subtype								
Group	Male	Female	Conv	SB	V	Sp	Lu	*F*	*T*	*M*	*P*	*A*	*Others*	GII	GIII	Death
YOUNG	0	2	2	0	0	0	0	1	1	0	0	0	0	0	0	0
ADULT	51	76	78	31	11	5	2	21	13	40	6	16	18	4	9	11
ELDERLY	30	31	49	9	0	2	0	7	23	41	1	7	9	5	1	14

Table Legends: M: male; F: female; Con: convexity; SB: skull base; V:ventricles; Sp: spine; Lu: Lung; GI: meningioma grade I; GII: meningioma grade II; GIII: meningioma grade III; *F*: fibrous subtype; *T*: transitional subtype; *M*: meningothelial subtype; *P*: peamomatosus subtype; *A*: angiomathosus subtype; *OT*: others subtypes.

demonstrated that undifferentiated vessels had few surrounding pericytes and were more apt to rupture. In addition, thin-walled dilated vessels, venous obstruction, and tumor infarction were also common in hemorrhagic meningiomas. Based on these observations, the tumor vasculature in meningiomas is heterogeneous, and undifferentiated vessels may play a pivotal role in the spontaneous intratumoral bleeding of meningiomas.

Haemorrhagic complications were always thought to be procedure-related, In this review, we verified six cases related to the previous embolization of these tumours, caused by intratumoral or peritumoral rupture of small vessels as a result of high injection pressure. Haemorrhagic complications occurred despite very careful technique. Therefore, such haemorrhage could also be due to some other unknown mechanisms. Likely, the most reasonable mechanism is that the vessels proximal to the site of microparticulate occlusion in these haemorrhage-prone tumours are fragile, and embolization causes increased blood pressure within these vessels, which subsequently rupture [24].

Although rare, major intracranial haemorrhage of meningiomas could have a dramatic effect on outcomes and may even be a life-threatening event, owing to acute increased intracranial pressure [1]. Haemorrhage associated with meningioma is associated with nearly 41 % mortality [1,25]. However, with a more comprehensive view, a lower mortality rate (13 %) was observed. The extent of haemorrhage and the status of consciousness before surgery are considered significant predictors of outcome. The key to success in these patients is early diagnosis and prompt surgical excision of the tumour and hematoma [1,4,25].

Compared to European or North American populations, meningioma bleeding has been considered more prevalent in Asia. Asian populations also appear to have a greater proportion of haemorrhagic stroke [26–28]. This may be because of the genetic differences in blood coagulation between Asians and non-Asians [29], and these genetic differences may minimally contribute to the ethnic difference in bleeding in meningiomas. Furthermore, in a recent report of meta-analysis on the incidence of intracerebral haemorrhage, the incidence was ≈2-fold higher in Asians compared to others ethnicities [30]. Despite these robust data, we have to take into account the possibility of under-reporting. Although intriguing, we must take into account the publication policy which may differ according to the region of the world, as well as the impact factor of the paper.

5. Conclusion

These tumours follow the histopathological distribution of meningiomas in general. The age distribution shows prevalence among the adult population but with a greater proportion in the elderly. The fact that the overwhelming majority is meningiomas with benign histological subtype is noteworthy. Another relevant factor observed is that most reports are from patients of Asian origin, which can be a risk factor for tumour haemorrhage in that population.

6. Limitations

Although this study had a large sample size, its limitations should be mentioned. Information on the extent of tumour resections, clinical description (duration of symptoms) were obtained following the description of the article, as each author classified the degree of

resection (if through image examination, or only for surgical findings), was not specified in those articles. Most of the articles do not present detail of this topic, being a major impeding factor in this analysis

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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Análise crítica

Características dos meningiomas segundo a faixa etária

Considera-se que os meningiomas em pacientes jovens diferem significativamente de suas contrapartes adultas (47). Os meningiomas intracranianos constituem uma porcentagem surpreendentemente baixa (0,4 - 4,6%) de tumores cerebrais entre jovens, enquanto são o tumor cerebral benigno mais comum entre adultos (48). Os meningiomas pediátricos também diferem da apresentação em adultos, com predileção no sexo masculino, com presença de alterações císticas, associados com maior frequência à neurofibromatose, sendo de alto grau de malignidade e com ausência de fixação dural (49).

Modan et al. revisaram retrospectivamente cerca de 11.000 pacientes submetidos à radiação para tinea capitis quando crianças (50), e observaram um aumento de 4 vezes na incidência de meningioma nestes pacientes. Os meningiomas ocorreram tipicamente acima de 10 anos após o tratamento. Similarmente, um intervalo médio acima de 20 anos entre o diagnóstico primário de câncer e o diagnóstico de meningioma foi relatado em grandes estudos de coorte de sobreviventes de câncer infantil (51, 52). Além disso, este risco não se estabilizou ao longo do tempo (53), mas houve aumento do risco com o aumento das doses de radiação (52, 54), embora o impacto do volume craniano irradiado exposto não tenha sido estudado e possa ser considerado em estudos futuros. Alguns estudos relataram que quanto menor a idade do diagnóstico de câncer na infância, maior o risco de meningioma (55-57), o que pode ser devido a uma maior sensibilidade à radiação, como observado em outros tecidos (por exemplo, na glândula tireóide) (57). Curiosamente, observamos dois picos de incidência de meningioma entre pacientes jovens e na sexta década entre adultos que são coincidentes com o aumento e a diminuição respectivamente dos hormônios sexuais. O impacto da flutuação hormonal não foi totalmente explorado nos pacientes com meningiomas e poucos estudos fornecem detalhes sobre o estado pós-menopausa em relação à presença e duração da terapia de reposição hormonal (58). A influência hormonal também foi interessante na população masculina, nos quais se observou um índice médio de massa corporal mais alto e taxas mais altas de obesidade em pacientes do sexo masculino com meningiomas (59).

A incidência proporcionalmente alta de meningiomas GII-GIII em pacientes com menos de 20 anos, tanto na base do crânio quanto na convexidade, foi observada em

comparação aos adultos. Os meningiomas malignos foram predominantemente descritos na base do crânio nos adultos (25, 26).

Os meningiomas pediátricos e / ou associados à mutação no gene neurofibromina 2 (*NF2*) são nitidamente incomuns em adultos com tumores esporádicos (60). Os pacientes com mutação de *NF2* que apresentam início dos sintomas da doença durante a infância têm muito mais probabilidade de apresentar meningiomas do que os pacientes mais velhos com mutação *NF2* (61). A associação de mutação de *NF2* com meningiomas pediátricos também foi evidenciado em outras séries, sendo observado em 7 a 41% dos pacientes (62-66).

Meningiomas intraventriculares

A origem embriológica distinta das meninges no sistema nervoso central pode explicar as diferenças nas distribuições histológicas do meningioma. As meninges que cobrem o tronco cerebral e a medula espinhal surgem de uma linhagem embriológica claramente diferente das meninges da convexidade cerebral. Essa diferença embriogênica também pode estar implicada na predominância observada do subtipo meningotelial no neuroeixo central, por exemplo (29).

A origem embriológica dos tumores ventriculares é completamente diferente daquela em outros locais. Os meningiomas surgem das células das aracnóides, as células especializadas nas granulações aracnóides. Da mesma forma, meningiomas intraventriculares (MIVs) surgem de células aracnóides presentes no plexo coróide (67). Interessantemente, observamos uma proporção maior de subtipos fibrosos nos MIVs, onde a sua frequência foi de 39,7%. Vale ressaltar que os tumores fibrosos, de acordo com nossa revisão, mostraram comportamento mais agressivo do que outros subtipos de meningiomas grau I. Observou-se mais metaplasia maligna e progressão tumoral em tumores originalmente fibrosos (68, 69); recorrência tumoral no local cirúrgico (70); carcinomatose no LCR (71) e outros órgãos (72) e associação a presença de hemorragia intratumoral (73-76). Adicionalmente, os tumores fibrosos apresentaram maior taxa de mortalidade e recorrência tumoral que os demais subtipos de meningiomas.

Embora os MIVs apresentem uma localização anatômica peculiar, com íntima relação com os seios venosos e importantes estruturas neuronais, como as vias visuais, que representam um grande desafio para os cirurgiões, o manejo neurocirúrgico tem sido

a melhor opção terapêutica para este tipo de tumor (77). A ressecção microcirúrgica completa dos MIVs tem proporcionado resolução significativa dos sintomas após a remoção da lesão (78) e apesar das dificuldades técnicas, tem-se observado alta taxa de ressecção total da lesão (95,1%) com baixa taxa de mortalidade (4%). A alta taxa de ressecabilidade total do tumor decorre da presença de um plano de clivagem cirúrgica nos MIVs em comparação aos tumores em outras localizações, e garante uma menor taxa de recorrência tumoral.

Meningiomas espinais

A revisão sistemática dos meningiomas espinais (ME) mostrou que estes ocorrem com mais frequência na região torácica em mulheres de meia idade (79, 80), e o resultado cirúrgico do tumor foi excelente, mesmo em pacientes que apresentavam um estado neurológico pré-operatório ruim (81). A abordagem cirúrgica ideal para ME variou de acordo com a localização e extensão do tumor. A laminectomia ou a hemilaminectomia em um ou dois níveis foi adequada para a maioria dos tumores dorsal e dorsolateral, mas foi necessária uma exposição mais lateral para os tumores com localização ventro-lateral ou ventral à medula espinhal. Uma costo-transversectomia ou vertebrectomia parcial mostrou-se necessária para melhorar a exposição do tumor e permitir uma remoção mais segura (82).

A taxa de recorrência do ME foi baixa (4,35%), semelhante à taxa observada em meningioma ventricular (41). A incidência da recorrência de ME variou de 1,3% a 6,4% e abrangeu um período de 1 a 17 anos (81). A ressecção parcial foi indicada como co-fator determinante na recorrência tumoral (79), mas a remoção subtotal do tumor não levou necessariamente à recorrência (83). Os subtipos de ME atípico ou anaplásico associaram-se ao aumento da recorrência (80, 84, 85). O tratamento cirúrgico dos MEs recorrentes impôs desafios devido à presença de cicatrizes aracnóides, que dificultaram as ressecções radicais e aumentaram a recorrência do tumor.

A taxa de mortalidade em ME na presente revisão foi baixa (3%). De fato, a morbimortalidade pós-operatória diminuiu progressivamente com o advento de modalidades sofisticadas de neuroimagem, técnicas neuroanestésicas, microcirúrgicas, uso de ultrassonografia intraoperatória, microscópios operatórios, aspiradores cirúrgicos ultrassônicos, angiografia, embolização intravascular pré-operatória e monitoramento

funcional da medula espinhal (81, 86, 87). As principais causas de morte no período pós-operatório (82) na série revisada incluíram embolia pulmonar, pneumonia aspirativa, acidente vascular cerebral e infarto do miocárdio (83, 88). Nesse contexto, os esforços de deambulação e reabilitação devem ser priorizados no pós-operatório inicial, e um regime de redução da terapia com esteroides deve ser instituído (89) precocemente, sempre que possível.

Meningiomas múltiplos

Os meningiomas múltiplos (MMs) são mais comuns em mulheres, e essa predileção de gênero é significativamente maior (3,5F: 1M) do que a observada nos casos de meningiomas únicos (90-92), nos quais a proporção de gênero varia, mas é de aproximadamente 2F: 1M (93-95). A razão dessa distribuição desequilibrada de gênero permanece incerta; no entanto, maior expressão de progesterona identificada nesses MMs do que nos meningiomas únicos pode ser responsável pela preponderância feminina nos casos de MMs (91, 96). Os MMs são raramente encontrados na infância e na adolescência (92, 97).

Larson et al. (98) e von Deimling et al. (99) relataram que os MMs podem ter surgido a partir de uma única célula progenitora, que se disseminou pelo espaço subaracnóideo. No entanto, outros afirmam que os MMs se originam de múltiplos focos e não são o resultado da migração celular através do espaço subaracnóideo (100-102). As alterações moleculares nos MMs diferem, dependendo de serem esporádicos, induzidos por radiação ou casos familiares (98, 103, 104). Os MMs estão associados à presença de outros tipos de tumores sólidos em várias síndromes familiares, como neurofibromatose tipo 2, síndrome do carcinoma basocelular nevóide, síndrome de Cowden e síndrome de Werner (105).

A abordagem terapêutica para o tratamento de MMs inclui cirurgia, radiação cerebral total e radiocirurgia estereotáxica, apesar de dados conflitantes na literatura (106). Benefícios e riscos gerais devem ser considerados na seleção do tratamento, como, por exemplo, os efeitos de radiação agudos, subagudos e retardados em um paciente jovem e ativo (107). A cirurgia continua sendo o tratamento de escolha e deve ser indicada para meningiomas sintomáticos maiores que 3cm, com acessibilidade cirúrgica, crescimento acelerado ou presença de edema peritumoral (92, 108, 109). No entanto, os

benefícios de procedimentos cirúrgicos agressivos, para reduzir a recorrência, têm sido objeto de debate na literatura (110), uma vez que a maioria dos tumores analisados, incluindo os de nosso estudo, eram pequenos e assintomáticos. O prognóstico para pacientes com MMs foi bom e não diferiu significativamente do meningioma solitário, exceto nos casos de MMs induzido por radiação e meningiomas associados à neurofibromatose com mutação no gene da neurofibromina 2 (*NF2*) em crianças (90, 108).

Meningiomas hemorrágicos

Embora os meningiomas sejam as lesões intracranianas benignas mais comumente encontradas, sendo responsáveis por cerca de um quarto de todas as lesões tumorais intracranianas primárias, a incidência de hemorragia nestes tumores é muito baixa, aproximadamente 1.3% (111-113). A hemorragia em um meningioma pode se manifestar de várias maneiras, incluindo hemorragia subaracnóide (comumente observada em meningioma parassagital e falcino) (114), hemorragia intracerebral e, menos comumente, hemorragia intratumoral (111). Descrições prévias relatam que o hematoma subdural, associado a meningioma de localização na convexidade, é observado raramente (112). No entanto, esta revisão sistemática demonstrou que o hematoma subdural foi o segundo tipo de sangramento mais prevalente associado ao meningioma (27,36%).

Os mecanismos de sangramento intratumoral ainda são controversos e incluem ruptura de vasos sanguíneos tumorais, necrose tumoral e invasão do parênquima cerebral. O crescimento capilar em tumores cerebrais foi classificado em três grupos: axial, retiforme e glomerulóide. Foi relatado que a maioria dos tumores continha uma combinação desses tipos capilares, mas apenas o tipo retiforme foi associado de modo significativo à hemorragia intratumoral (115). Entretanto, muitos outros mecanismos foram também propostos como enfraquecimento progressivo dos vasos parietais devido à variação no suporte do estroma tumoral, ruptura / distorção dos vasos pelo tumor, hipertensão venosa, proliferação endotelial com oclusão vascular secundária, formação de vasos sanguíneos anormais, mesmo em meningiomas benignos, estiramento de veias em ponte do tumor com ruptura subsequente com ou sem trauma, liberação de substância vasoativa intratumoral (por exemplo, histamina) e fragmentação direta de meningioma

com sangramento (19). A aparente discrepância nos mecanismos propostos para explicar a hemorragia poderia ser decorrente, em parte, pelo fato de a vasculatura tumoral ser heterogênea e a utilização de marcadores vasculares distintos em cada estudo. A heterogeneidade vascular foi identificada previamente no câncer de próstata, câncer de pulmão e carcinoma de células renais por meio de vários marcadores vasculares (116-118). Por exemplo, 2 tipos distintos de vasos sanguíneos foram identificados no carcinoma de células renais: vasos indiferenciados ($CD31^+/CD34^+$) e vasos diferenciados ($CD31^+/CD34^-$). Mais importante ainda, apenas os vasos indiferenciados tiveram uma correlação significativa com tumores mais malignos (118). Outra explicação seria o aumento da possibilidade de infarto intratumoral com subsequente hemorragia intratumoral em decorrência do crescimento tumoral. Este também poderia ser um evento importante no processo de hemorragia peritumoral. Outras causas subjacentes, como trombose, edema da parede vascular e erosão dos vasos poderiam eventualmente causar o infarto. Algumas condições estressantes, como convulsão e rápida mudança na pressão sanguínea poderiam atuar como fatores contribuintes para o estabelecimento da trombose dos vasos intratumorais, do infarto tumoral ou da dilatação dos vasos peritumorais. Haveria o argumento de que o infarto intratumoral não seja a causa da hemorragia, mas a consequência. No entanto, o infarto intratumoral geralmente não ocorreu em casos de hematoma peritumoral, e a dilatação peritumoral dos vasos não poderia causar o infarto (111).

Há uma tendência de se associar as ocorrências hemorrágicas ao procedimento terapêutico de meningiomas. No entanto, verificamos nesta revisão que as complicações hemorrágicas ocorreram apesar da técnica muito cuidadosa, no entanto a incidência de complicações foi baixa sendo relatado em apenas seis casos de hemorragias relacionadas à embolização prévia do tumor, causada por ruptura intratumoral ou peritumoral de pequenos vasos em decorrência de alta pressão de injeção. Portanto, outros mecanismos ainda desconhecidos levariam a hemorragia em meningiomas. Hipotetiza-se que haja uma condição prévia de fragilidade propensa a hemorragia nos vasos proximais ao local da oclusão microparticulada nesses tumores, e a embolização causaria aumento da pressão arterial dentro desses vasos, que subsequentemente se romperiam (119).

Embora rara, a hemorragia intracraniana em meningiomas pode causar um efeito dramático nos resultados, sendo um evento com risco de vida devido ao aumento agudo

da pressão intracraniana (114). De fato, tais eventos hemorrágicos estiveram associados a cerca de 41% de mortalidade (114, 120). A extensão da hemorragia e o estado de consciência antes da cirurgia foram considerados preditores significativos do resultado. A chave para o sucesso do desfecho nesses pacientes foi o diagnóstico precoce e a excisão cirúrgica imediata do tumor e do hematoma (114, 120, 121).

Em comparação com as populações europeias ou norte-americanas, o sangramento de meningioma foi considerado mais prevalente em asiáticos. Esta população apresenta também uma proporção maior de acidente vascular cerebral hemorrágico (122-124). Isso poderia ser devido às diferenças genéticas na coagulação do sangue entre asiáticos e não asiáticos (125), o que poderia justificar parcialmente a diferença étnica na prevalência de sangramento nos meningiomas. A meta-análise recente sobre hemorragia intracerebral relatando uma incidência cerca de 2 vezes maior em asiáticos em comparação com outras etnias (126) corrobora os achados desta nossa revisão quanto à distribuição étnica de hemorragia em meningiomas. Apesar deste dado corroborativo, devemos, ainda, levar em consideração a possibilidade de subnotificação que pode diferir conforme a região do mundo.

Impacto da radioterapia na recorrência em nossa casuística e na literatura

PUBLICAÇÃO 6

Título	Atypical and Malignant Meningiomas: Neurooncologic Management in a Brazilian cohort		
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Revista	World Neurosurgery		
Submetido	01/08/2017	**Aceito**	26/09/2017
Citação completa	Pereira BJA, de Almeida AN, de Aguiar PHP, Paiva WS, Cabrera HN, da Silva CC, Teixeira MJ, Marie SKN. Atypical and Malignant Meningiomas: Neurooncologic Management in a Brazilian cohort. World Neurosurg. 2018 Feb;110:e20-e23. doi: 10.1016/j.wneu.2017.09.172. Epub 2017 Nov 28. PMID: 29196252.		
Fator de Impacto	1.723		
Citações	Scopus:5 ; Web of Science: 5; Google scholar: 8		

Atypical and Malignant Meningiomas: Neurooncologic Management in a Brazilian cohort

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OBJECTIVE: To analyze the surgical and oncologic treatment of a Brazilian cohort of patients with grade II and III meningioma at a follow-up time of 15 years to get an overview of these patients' outcomes.

METHODS: Cross-sectional study of 43 patients (26 women, 17 men; age range 20 to 83 years; average 57.72 ± 14.54) operated on from 2000 to 2014 at a single institution, with the neuropathologic diagnosis of meningioma grade II (39 patients) and grade III (4 patients).

RESULTS: Radiotherapy: 24 patients (55.81%) underwent radiotherapy; the time between the surgical procedure and the beginning of radiotherapy was 5 months; 7 patients with a diagnosis of AM underwent a new surgical procedure, albeit of adjuvant therapy, because of tumor recurrence, and only 3 of them underwent radiotherapy after the first resection. Mortality: in total, 19 deaths (44.18%) were identified in this sample: 15 (38.46%) with GII and 4 (100%) with GIII. The 10-year survival was expected in 35% of GII patients and 0% of GIII patients.

CONCLUSION: Surgery is still the main form of treatment and the mainstay for prolonging survival. Radiotherapy is still controversial; however, we observed its positive impact on recurrence and progression-free survival.

Key words
- Atypical meningioma
- Malignant meningioma
- Progression-free survival

Abbreviations and Acronyms
AM: Atypical meningioma
GI: Grade I meningioma
GII: Grade II meningioma
GIII: Grade III meningioma
GTR: Gross total resection
MM: Malignant meningioma
STR: Subtotal resection

INTRODUCTION

Meningioma is the most common nonglial primary intracranial brain tumor, with an incidence rate of 13% to 19% in large series of primary intracranial tumors.[1] Although meningiomas are handled as benign lesions, a substantial proportion of them display more aggressive behavior,[2] with quoted incidences varying widely from 1.5% to 35% of all meningiomas.[3,4]

Clinical criteria to guide the aggressiveness of a complementary therapy after subtotal resection (STR) or gross total resection (GTR) in patients with atypical meningioma(AM) grade II and malignant meningioma (MM) grade III are not well established. Therefore, it will be helpful to identify the clinical, radiographic, or surgical factors that are associated with disease progression after STR or GTR[5] to assist in choosing between aggressive and more conservative complementary treatments with the preservation of neurologic function, especially for tumors in critical locations.

The objective of this study was to analyze the outcome in patients with histopathologic diagnoses of World Health Organization grade II and III meningiomas, focusing on their surgical and oncologic management in a 15-year follow-up of a single-institution cohort, and to determine potential factors that are predictive of outcome.

METHODS

At the University of São Paulo, 629 patients underwent surgical treatment for brain tumors in a 15-year period (2000–2014) and received a neuropathologic diagnosis of meningioma. A detailed, retrospective analysis was performed on 43 patients

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Citation: World Neurosurg. (2018) 110:e20-e23.
https://doi.org/10.1016/j.wneu.2017.09.172

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

(26 women, 17 men) whose ages ranged from 20 to 83 years (average, 57.72 ± 14.54 years), who were classified as having grade II meningioma (GII, 39 patients) or grade III (GIII, 4 patients), based on the 2016 World Health Organization meningioma grading criteria.[6] These patients were treated by the Neurosurgery Group of the Department of Neurology at the Hospital das Clínicas of the School of Medicine at the University of São Paulo.[7] Patients with less than 12 months of follow-up time were excluded.

The hospital database system keeps records of all patients and dates related to medical appointments, surgical procedures, radiotherapy sessions, emergency room admissions, and in-hospital deaths. Clinical data (Karnofski Performance Scale, neurologic status, and medicines in use) and information about out-of-hospital death were obtained through attendance or phone interviews. Interviewees were also asked whether the patients had improved, remained stable, or worsened after surgery. As surgical factors, the extent of tumor resection (STR or GTR) and the site of the tumor were considered. Radiotherapy and mortality were analyzed as complementary treatment and final outcome, respectively.[7] This study was approved by our Institutional Review Board under registration CAPPESq # 200/05.

RESULTS

Atypical Meningiomas (Recurrence and Radiotherapy)

Among the 39 grade II AM patients (25 women, 14 men), the ages ranged from 20 to 82 years (57 ± 14.4 years).

In this sample, 22 patients (56.41%) were to receive complementary radiotherapy beginning 1 to 24 months (mean, 4 months) after the surgery. Six of those 22 patients (27%) experienced recurrence within a time interval ranging from 4 to 104 months (3.6 ± 3.0 years), in spite of the complementary therapy. Three of these 6 patients with recurrence died after 5 to 9 years of follow-up (7.0 ± 2.0 years), and the other 3 are still alive after a follow-up time of 2 to 10 years (5.2 ± 4.3 years). Among the remaining 16 patients who received radiotherapy and did not experience tumor recurrence, 14 patients are still alive, with a mean follow-up time of 4.4 ± 2.1 years.

Seventeen of the 39 patients did not receive radiotherapy, and among them, 8 patients (mean age, 57.82 ± 12.48 year) died within the first year after the surgery. Except for 2 patients, 1 of whom experienced recurrence and died 2 years after surgery and another 2 who died 3 years after surgery, the remaining 7 patients are still alive, with a follow-up time of 5.4 ± 3.4 years (Table 1).

Malignant Meningiomas

Four patients with grade III MM (1 woman, 3 men) presented an overall survival time of 0.8 year, and only 1 patient had time to undergo radiotherapy.

Mortality

The overall mortality, including both AM and MM, was 19 deaths of 43 patients (44%): 15 (38%) in AM patients and 4 (100%) in MM patients. In both grades II and III, 10 of 43 tumor-related deaths (23%) occurred within the first year after surgery (7 in AM patients and 3 in MM patients), and only 1 patient died of causes not related to the tumor.

Resection Sites

Meningiomas in the brain convexity were more frequent among grade II patients (17/39, 43.58%), followed by meningiomas at the base of the skull (sphenoid wings, petroclival region, middle fossa, and anterior fossa) (10/39, 25.59%), whereas no predilection of localization was observed in the 4 MM patients.

The localization of the meningioma did not appear to impact patient outcome.

Inasmuch as the study was retrospective, the present analysis presents some weakness regarding the degree of surgical resection of these tumors. The extent of tumor surgical removal was evaluated through the Simpson grade in only 30% of the patients. However, the available data allow us to conclude that this variable did not present a statistical difference in the present cohort.

DISCUSSION

Surgery is the treatment of choice for meningioma. The refinement of neurosurgical approaches and better understanding of the anatomy allow for a more radical tumor resection. Furthermore, more detailed neuroimaging techniques have also allowed for improvement in preoperative planning. Surgical excision of the tumor and its implanted dural base is the most common type of management. However, many tumors cannot be totally resected because they envelope vital neural or vascular structures or present as excessive plaque.[8]

Although meningiomas were historically considered radioresistant,[9] radiotherapy has been shown to improve the local control of AM and MM.[10] Nevertheless, controversial issues remain, particularly about AM management in terms of the optimal dose and timing of this complementary therapy when GTR is achieved. By contrast, radiotherapy after STR of AM is included as a standard of care in many treatment protocols, although there is no such consensus.[11,12] Debates still persist on whether all AM should be treated by radiotherapy and on whether radiotherapy should be limited to subtotally resected tumors or applied only after revision surgery.[13,14]

As a result, clinical outcome predictive factors are needed to guide therapeutic protocols.

In the present cohort of 39 patients with grade II AM, 22 patients were treated with complementary radiation therapy; at the endpoint of around 4.8 years of follow-up, 77% (17/22) of those patients are still alive, in contrast to the 41% (7/17) of patients who did not receive radiotherapy in a follow-up time of 5.4 years. In a first analysis, independent of the recurrence rate, it seems worthwhile to have patients with diagnoses of AM undergo complementary radiation therapy. However, if we exclude the 7 patients who died within the first year after surgery from the 17 patients who did not undergo radiotherapy, 7 of 10 patients (70%) are still alive in a follow-up time of 5.4 years, even without receiving complementary therapy. Therefore, it seems crucial to search for predictive markers to recognize those critical AM patients who are likely to die within the first year of disease evolution and then provide them with a more aggressive complementary therapy to improve their clinical outcome.

Factors such as age, gender, and tumor site were not shown to have any impact on the outcome. Thus, other biologic markers, such as molecular signature, should be searched to this end. Such

Table 1. Results in 39 Patients with Grade II Atypical Meningioma

	Radiotherapy				
	Yes (n = 22)		No (n = 17)		
	Recurrence				
Variable	Yes (n = 6)	No (n = 16)	Yes (n = 2)	No (n = 15)	
At recurrence (years)	3.6 ± 3.0	-	2.2 ± 1.4	-	-
Mortality	3	2	2	7	1
At overall survival (years)	7.0 ± 2.0	2.3 ± 1.1	2.5 ± 0.7	0.5 ± 0.5	3.0
In follow-up	3	14	0	7	
At follow-up (years)	5.2 ± 4.3	4.4 ± 2.1	0	5.4 ± 13.4	

exploration is more urgent for MM, wherein a fatal outcome was observed in 100% of the cases.

In contrast to benign meningiomas, grade II/III tumors demonstrate more complex cytogenetic and molecular profiles with the activation of oncogenes, inactivation of tumor suppressor genes, and alterations in other genes that are involved in several molecular pathways,[15] such as expression of matrix metalloproteinase, which has been studied in meningioma with respect to tumor invasiveness, malignancy, and recurrence. A further understanding of the genes and signalling pathways associated with meningioma formation, growth, and transformation is likely to provide a foundation for the future assessment of histologic and clinical behaviors and responses to potential gene therapies and individualized treatment regimens.[16]

CONCLUSIONS

Surgery is still the primary form of treatment for meningiomas, given that it is the mainstay for prolonging survival. However, although radiotherapy is still a controversial issue, it was shown to have a positive impact when tumor recurrence and progression-free survival were analyzed.

Limitations

Although this study had a relatively large sample size, its limitations should be mentioned. Information on the extent of tumor resections is a limitation of our study because some surgical reports are not congruent with the postoperative images, and in other situations, a postoperative image examination was not requested or was not found owing to a change in the institution's image visualization system during this period; therefore, the information about the degree of surgical resection in some cases is not available.

ACKNOWLEDGEMENTS

The authors thank Ms. Ivoneide Estevão for secretarial assistance; the surgeons Dr. Marcos Queiróz Gomes Teles, Dr. Marcos Maldaum, and Dr. Pedro Santana (in memoriam); the pathologists Dr. Sergio Rosemberg and Dr. Fernando Frasseto; and the radiologists Claudia Leite and Luis Filipe Godoy.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 1 August 2017; accepted 25 September 2017

Citation: World Neurosurg. (2018) 110:e20-e23.
https://doi.org/10.1016/j.wneu.2017.09.172

Journal homepage: ***www.WORLDNEUROSURGERY.org***

Available online: ***www.sciencedirect.com***

PUBLICAÇÃO 7

Título	Impact of radiotherapy in atypical meningioma recurrence: literature review		
Autores	Benedito Jamilson Araujo Pereira, Antonio Nogueira de Almeida, Wellingson Silva Paiva, Manoel Jacobsen Teixeira, Suely Kazue Nagahashi Marie		
Revista	Neurosurgical review		
Submetido	09/01/2018	**Aceito**	20/02/2018
Citação completa	Pereira BJA, de Almeida AN, Paiva WS, Teixeira MJ, Marie SKN. Impact of radiotherapy in atypical meningioma recurrence: literature review. Neurosurgical review. 2019;42(3):631-7. doi: 10.1007/s10143-018-0959-8.		
Fator de Impacto	2.532		
Citações	Scopus: 10; Web of Science: 9; Google scholar: 13		

Neurosurgical Review
https://doi.org/10.1007/s10143-018-0959-8

REVIEW

Impact of radiotherapy in atypical meningioma recurrence: literature review

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Received: 9 January 2018 / Revised: 29 January 2018 / Accepted: 20 February 2018

Abstract
Evaluate whether radiotherapy (RT) after the neurosurgical treatment of atypical meningiomas (AM) has an impact on the reduction rate of recurrence. A Medline search through October 2017 using "atypical meningioma" returned 1277 papers for initial review. Inclusion criteria were as follows. We analyzed the database and included articles in which the anatomic pathological classification of atypical meningiomas was in accordance with WHO 2007 or WHO 2016 criteria, patients > 18 years of age, and there was postoperative external beam radiation to the tumor bed. Exclusion criteria were WHO grade I or III meningioma, patients who underwent whole-brain radiation, RT used as salvage therapy for recurrence, palliative dose of RT (< 45 Gy), recurrent AMs, and multiple AMs. Papers reporting outcomes in which atypical and anaplastic meningiomas were analyzed together were rejected, as were papers with small samples that may compromise evaluation. After filtering our initial selection, only 17 papers were selected. After reviewing the seventeen articles including a total of 1761 patients (972 female and 799 male; 1.21 female/1.0 male), the difference in proportion of tumor recurrence between patients with and without radiotherapy after neurosurgical procedure was 1.0448, 95% CI [0.8318 to 1.3125], p value = 0.7062. On the basis of this review, there is no evidence to suggest that RT decreases the rate of recurrence in patients with atypical meningiomas.

Keywords Atypical meningioma · Radiotherapy · Recurrence

Introduction

Atypical meningiomas (AM) represent up to 8% of all meningiomas [1], and their incidence is increasing (> 5–10% among all types of meningiomas); however, this number should increase given the new World Health Organization (WHO) 2016 criteria for the classification of this subtype of meningioma [2]. In fact, AM account for 20–25% of recurrent meningiomas [3, 4].

The rationale for advocating gross total resection (GTR) as the primary treatment for meningiomas is attributed to effective local control post-GTR and avoiding the toxicity associated with postoperative radiation therapy, including the increased risk of radiation-induced malignancies [5]. In neuro-oncological management, complete resection must be pursued in this subtype of tumor [6], and a definitive cure after surgical resection is achieved in 16–18% of patients. Nevertheless, the disease will recur within a few months in up to 62–69% of cases [7, 8].

Adjuvant radiotherapy after the surgical resection of AM continues to be controversial. Compared to surgery alone, surgery followed by postoperative radiation lowers the incidence of local recurrence of AM, as reported in previous reviews [9]. However, opposite results have also been reported [10, 11]. In a recent retrospective case study of 45 patients with atypical meningioma, Endo et al. [11] showed no additional benefit of adjuvant radiotherapy concerning the long-term tumor control; results similar to those of Champeaux et al. [10], who showed that patients who received radiotherapy did not have a different overall survival nor difference in recurrence rate.

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Published online: 19 March 2018

Among the forms of radiotherapy treatment, we also did not observe consensus on the techniques. During the last two decades, stereotactic radiosurgery (SRS) has proved to be an effective treatment for WHO grade I benign meningioma [12, 13]. However, the efficacy of SRS in the treatment of grade II atypical meningiomas is still unclear [14]. Gamma knife radiosurgery (GKRS) for higher-grade meningiomas has been less well studied [15]. In the setting of recurrent atypical or malignant meningiomas, GKRS may provide durable palliation and local control for some but with poor long-term control overall [16].

Given the conflicting reports in the literature, we performed a systematic review to assess the impact of radiotherapy (RT) combined with surgical resection on the recurrence rate in patients with AM.

Methods

A Medline search from 2010 to October 2017 using "atypical meningioma" returned 1277 papers; we based our revision on this initial corpus. As a first selection step, we adopted the following inclusion criteria: (1) reports in which the anatomic pathological classification of AM was in accordance with WHO 2007 [17] or 2016 [2] criteria, (2) patients older than 18 years of age, and (3) postoperative external beam radiation to the tumor bed. Exclusion criteria were WHO grade I or III meningioma, patients who underwent whole-brain RT, RT used as salvage therapy for recurrence, definitive RT, palliative dose of RT (< 45 Gy), recurrent AMs, and multiple AMs.

All papers reporting outcomes in which atypical and anaplastic meningiomas were analyzed together were excluded, as were reports in the format of case reports with small series. Seventeen papers fulfilled the above criteria, and these papers gathered data from 1761 patients, on whom the present analysis of the neuro-oncological management of AM was based.

Data evaluation

The patients' clinical data and tumor-evolution (recurrence or not) data were tabulated, mainly, the data concerning tumor recurrence after neurosurgical procedure and the impact of RT in terms of preventing tumor recurrence in AM [see Fig. 1 for the PRISMA study flow diagram].

We calculated the weighted mean differences and the 95% confidence interval (CI). Dichotomous variables were presented as odds ratios (ORs) with a 95% CI. Matched analysis was performed as appropriate. Significance was set at $p < 0.05$.

Results

A total of 1761 patients (972 female and 899 male; 1.21 female/1.0 male ratio) reported in 17 manuscripts from worldwide centers during the period from 2010 to October 2017 were selected for the present analysis. Although the majority of the selected studies were from centers in the USA, we managed to analyze studies from each continent (see Table 1). Among them are 573 patients who underwent RT (32.5%) with a recurrence rate of 26% (149 patients). Comparatively, of the 1188 patients who were initially treated only with surgery, 299 patients presented tumor recurrence (25.16%). Thus, the difference in tumor recurrence between the two groups treated and not treated with RT after neurosurgical procedure was not significant (1.0448, 95% CI [0.8318 to 1.3125], p value = 0.7062) (see Table 1 and Fig. 2).

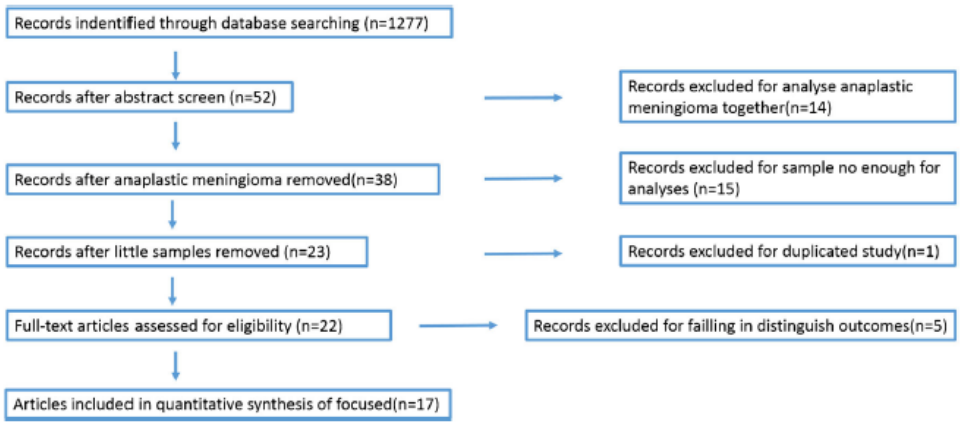

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study flow diagram

Table 1 Literature review

Author/year	RT without recurrence	RT with recurrence	RT total	No RT without recurrence	No RT with recurrence	No RT total	Male	Female	Country	Odds ratio	95% CI	*p*
Jo 2010 [18]	19	3	22	9	4	13	18	17	South Korea	2.25	0.4348 to 11.7084	0.3327
Komotar 2012 [19]	12	1	13	19	13	32	20	25	USA/Australia	5.28	0.6253 to 44.6056	0.1263
Lee 2013 [20]	28	3	31	45	14	59	34	56	USA	2.45	0.6546 to 9.1842	0.1831
Park 2013 [9]	21	6	27	32	24	56	33	50	South Korea	1.92	0.7055 to 5.2718	0.2005
Zaher 2013 [21]	22	4	26	6	12	18	22	22	Egypt	4.33	1.2033 to 15.6056	0.0249
Hardesty 2013 [22]	56	15	71	106	51	157	97	131	USA	1.53	0.8105 to 2.9169	0.1879
Sun 2014 [23]	30	9	39	108	4	112	63	88	USA	1.04	0.3182 to 3.4298	0.9426
Aizer 2014 [24]	30	4	34	38	19	57	41	50	USA	2.83	0.8892 to 9.0279	0.0782
Hammouche 2014 [25]	26	10	36	29	14	43	43	36	UK	11.721	0.4650 to 2.9542	0.7364
Yonn 2015 [26]	15	8	23	118	17	135	72	86	USA	0.3620	0.1401 to 0.9357	0.0360
Bagshaw 2016 [27]	17	3	20	16	23	39	28	31	USA	3.93	1.0520 to 14.6940	0.0418
Champeaux 2016 [10]	29	22	51	134	21	155	95	111	UK	0.3141	0.1597 to 0.6178	0.0008
Jenkinson 2016 [28]	27	9	36	74	22	96	67	65	UK/Ireland/Italy	0.9167	0.3860 to 2.1770	0.8437
Endo 2016 [11]	15	11	26	11	8	19	20	25	Japan/Egypt	0.9952	0.3360 to 2.9482	0.9931
Dohm 2017 [29]	42	21	63	38	14	52	45	70	USA	0.8077	0.3741 to 1.7436	0.5865
Pereira 2017 [30]	16	6	22	15	2	17	25	14	Brazil	0.4314	0.0772 to 2.4113	0.3383
Masalha 2017 [31]	19	14	33	91	37	128	76	85	Germany	1.8122	0.8232 to 3.9894	0.1397
Total	424	149	573	889	299	1188	799	962		1.0448	0.8318 to 1.3125	0.7062

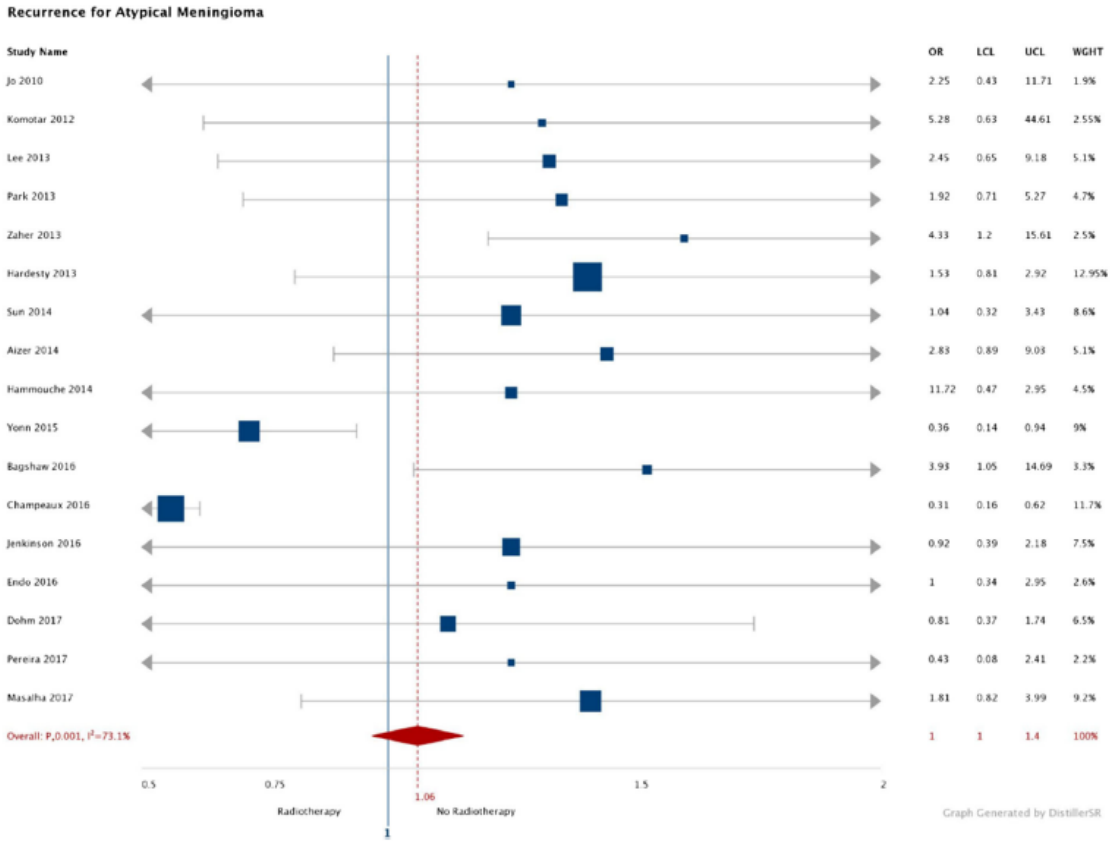

Fig. 2 Odds ratios of local control and recurrence in atypical meningiomas comparing surgery alone and surgery + RT among the studies

Discussion

Regarding the issue of the recurrence of meningiomas, some factors are already well established, such as the degree of surgical resection [32]. Since the initial work of Simpson [33] has proved that greater tumor resections lead to lower rates of tumor recurrence, other factors are still controversial, such as location. In our review, four of the articles selected [19–22] have an analysis of the subject, such as greater recurrence in tumors of convexity, but this result should reflect only the fact that this location is the most frequent. Despite technical and technological advances, the perioperative morbidity and mortality are high, because of their intimate anatomical relationship to the brain, cranial nerves, and essential blood vessels [34]. Another factor influencing the evolution of meningiomas is genetic alterations. Past studies have shown that the risk of meningioma recurrence is strongly correlated with the molecular profile of the tumor [35]. Genomic instability is one of the key differentiators between grade I and grade II–III meningiomas [36].

The clinical impact of AM recurrence is high, and the management of these patients poses specific challenges [37]. A robust analysis of large series of AM providing definitive guidelines for the neuro-oncological management of this type of meningioma is still missing; proof of this is that the management of these patients is still controversial and varies according to the group or center evaluated. In Germany, 74.1% of centers offer some form of RT following incomplete resection of AM, with 17.9% of centers offering postoperative RT even when tumor removal is complete [37]. In the UK, 59% of neurosurgeons would advise adjuvant radiotherapy in subtotal resection (STR), with only 20% doing so after gross total resection (GTR) [38]. Multicentricity varies from 19% at the first recurrence to 89% at the last follow-up, and marginal recurrence is progressively higher than the local type at the second and third recurrence, rendering management increasingly difficult [39, 40]. As the disease may be local, marginal, or distant with respect to the previous localization, a preferable indicator of treatment efficacy is disease-free interval [41, 42].

Radiotherapy was applied initially in the management of residual tumors after microsurgery. Its appropriate application proved to be successful when using all the available techniques, including linear accelerator (LINAC) [43–45], gamma knife [46, 47], proton beam [48], and conventional fractionated external beam radiation therapy (EBRT) [49]. As demonstrated in the literature, success rates of greater than 90% and with few associated complications can be achieved when stereotactic irradiation is performed in the management of intracranial meningiomas [16, 47, 50, 51]. The use of SRS alone has limitations that preclude its application in every case. These limitations are related to tumor size and proximity to eloquent structures especially the optic apparatus. Single-dose SRS is indicated for meningiomas smaller than 3 cm or 20 ml in volume and with a minimal distance from the optic apparatus of between 2 and 4 cm [52]. Although there are no long-term follow-up data for patients who underwent SRT for intracranial meningiomas, the expected success rate should be similar to that achieved using conventional EBRT, with fewer complications. A 5- and 10-year PFS rates of 92 and 83%, respectively, have been reported after EBRT [53]. The selection of the best treatment option for these lesions, however, should include consideration of tumor location, severity of presenting symptoms, and the long-term follow-up data of the available modalities.

There are several studies with conflicting results [9, 18, 19, 54, 55], and there are no randomized controlled trials, leading to a lack of class I evidence [56]. Our present systematic review failed to demonstrate a significant overall difference with respect to postoperative RT reducing tumor recurrence. However, there should be bias in the choice of patients who underwent radiotherapy, perhaps a point to be debated for future strategies to identify subgroups within the AM that present molecular characteristics at the level of biomarkers, so the patient is optimized and presents better results.

Conclusions

On the basis of this review, there is no evidence to suggest that RT decreases the rate of recurrence in patients with AM. Prospective studies on the effect of adjuvant RT for avoiding recurrence of AMs should be conducted to better address this question.

Limitations

Although this study had a large sample size, its limitations should be mentioned. Information on the extent of tumor resections, type of radiotherapy, and meningioma location is a limitation of our study; most of the articles do not present detail of these.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by our Institutional Review Board under registration CAPPESq no. 200/05.

Informed consent All authors agree to the publication guidelines of the Neurosurgical Review.

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Análise crítica

Na análise de nossa coorte de 39 pacientes com meningiomas de grau II (atípicos), 22 pacientes foram tratados com radioterapia (RT) complementar; no desfecho de seguimento médio de 68,8 ± 48,9 meses de acompanhamento, 77% (17/22) desses pacientes ainda estavam vivos, em contraste com 41% (7/17) dos pacientes que não receberam radioterapia neste mesmo período.

Relata-se que ao contrário dos meningiomas benignos, os tumores de grau II / III demonstram perfis citogenéticos e moleculares mais complexos com a ativação de oncogenes, inativação de genes supressores de tumores e alterações em genes envolvidos em várias vias moleculares (127), como a expressão da matriz metaloproteinase (MMP), que foi estudada no meningioma com relação à invasividade, malignidade e recorrência de tumores (128). Uma compreensão mais aprofundada dos genes e das vias de sinalização associadas à formação, crescimento e progressão maligna do meningioma provavelmente fornecerá uma base para a avaliação futura de comportamentos histológicos e clínicos e respostas a potenciais terapias genéticas e regimes de tratamentos individualizados (129).

A análise da nossa casuística, não nos permitiu concluir a efetividade da RT, corroborando com resultados prévios da nossa revisão literária sobre o assunto (130). Em uma primeira análise, parece interessante recomendar RT aos pacientes com diagnóstico de meningioma atípico (MA). Porém, se excluirmos os sete pacientes que morreram no primeiro ano após a cirurgia dos 17 pacientes que não foram submetidos à radioterapia, sete em cada 10 pacientes (70%) ainda estavam vivos em um período de acompanhamento de 5,4 anos, mesmo sem receber terapia complementar. Portanto, parece crucial procurar marcadores preditivos para identificar os pacientes críticos com MA que apresentem maior probabilidade de desfecho fatal no primeiro ano de evolução da doença para a indicação de uma terapia complementar mais agressiva para melhorar o resultado clínico final.

Parâmetros como idade, sexo e local do tumor não demonstraram ter nenhum impacto na evolução clínica tumoral. Assim, outros marcadores biológicos, como uma assinatura molecular, deverão ser pesquisados para esse fim. Essa exploração é mais urgente para meningiomas anaplásicos (grau III), onde um resultado fatal foi observado em 100% dos casos.

O impacto clínico da recorrência de MA é alto e o manejo desses pacientes apresenta desafios específicos (118). Ainda está faltando uma análise robusta de grandes séries de MA que forneçam diretrizes definitivas para o manejo neuro-oncológico desse tipo de meningioma. Prova disso é a variabilidade na descrição das estratégias terapêuticas de acordo com o grupo ou centro avaliado. Na Alemanha, 74,1% dos centros complementam o tratamento com alguma modalidade de RT, após ressecção incompleta da MA, e 17,9% dos centros aplicam RT no pós-operatório, mesmo quando a remoção do tumor é completa (131). No Reino Unido, 59% dos neurocirurgiões aconselham a RT adjuvante na ressecção subtotal, sendo que apenas 20% o fazem após a ressecção total (132). Estudos multicêntricos apresentam variação da indicação da RT de 19% na primeira recorrência a 89% no último acompanhamento, e o volume tumoral é progressivamente maior na segunda e terceira recorrências do que o do sítio original, tornando a conduta cada vez mais difícil (133, 134).

Existem vários estudos com resultados conflitantes (estudos mostrando resultados favoráveis ao uso da RT, bem como estudos sem resultados) (43, 135-138), e não existem ensaios clínicos randomizados, levando à falta de evidências de classe I (140). Nossa revisão sistemática atual não demonstrou uma diferença global significativa em relação à RT pós-operatória, reduzindo a recorrência do tumor. No entanto, deve haver viés na escolha dos pacientes submetidos à RT, o que pode justificar a falha terapêutica evidenciada nestes trabalhos. Eventualmente, um ponto a ser debatido para futuras estratégias para seleção dos pacientes com MA, seria a estratificação dos mesmos de acordo com características moleculares ao nível de biomarcadores de susceptibilidade a modalidades terapêuticas específicas, otimizando assim os desfechos clínicos.

Estudo das vias moleculares descritas em meningiomas

PUBLICAÇÃO 8

Título	Molecular alterations in meningiomas: Literature review		
Autores	Benedito Jamilson Araujo Pereira, Sueli Mieko Oba-Shinjo, Antonio Nogueira de Almeida, Suely Kazue Nagahashi Marie		
Revista	Clinical Neurology and Neurosurgery		
Submetido	29/09/2018	**Aceito**	06/12/2018
Citação completa	Pereira BJA, Oba-Shinjo SM, de Almeida AN, Marie SKN. Molecular alterations in meningiomas: Literature review. Clinical neurology and neurosurgery. 2019;176:89-96. doi: 10.1016/j.clineuro.2018.12.004		
Fator de Impacto	1.672		
Citações	Scopus: 9; Web of Science: 6; Google scholar: 11		

Clinical Neurology and Neurosurgery 176 (2019) 89–96

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Molecular alterations in meningiomas: Literature review

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ARTICLE INFO

Keywords:
Meningioma
Molecular
Mutation
Genetics

ABSTRACT

Meningiomas, tumors that originate from meningothelial cells, account for approximately 30% of all new diagnoses of central nervous system neoplasms. According to the 2016 WHO classification of central nervous system tumors meningiomas are classified into three grades: I, II, and III.

Past studies have shown that the risk of meningiomas recurrence is strongly correlated with the molecular profile of the tumor. Extensive whole-exome or whole-genome sequencing has provided a large body of information about the mutational landscape of meningiomas. However, such a stratification of meningiomas based on mutational analysis alone has been proven not to satisfy the clinical need for distinction between patients who need (or do not need) an adjuvant treatment.

Combined analysis of exome, transcriptome, methylome and future approaches for epigenetic aspects in meningiomas may allow researchers to unveil a more comprehensive understanding of tumor progression mechanisms and, consequently, a more personalized clinical approach for patients with meningioma.

A better understanding of the genetics and clinical behavior of high-grade meningiomas is mandatory in order to better design future clinical trials. By studying the mechanisms underlying these new tumorigenesis pathways, we should be able to offer personalized chemotherapy to patients with surgery and radiation-refractory meningiomas in the near future. The purpose of this article is to accurately bring the compilation of this information, for a greater understanding of the subject.

1. Introduction

Meningiomas, tumors that originate from meningothelial cells, account for approximately 30% of all new diagnoses of central nervous system neoplasms [1]. According to the 2016 WHO classification of central nervous system tumors [2], meningiomas are classified into three grades: I, II, and III. The grade I meningiomas are typical or benign, stratified into nine histological subtypes including meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lympho-plasmacyte-rich, and metaplastic, and represent 88–94%, of all meningiomas [3]; atypical meningiomas are "intermediate grade" malignancies (grade II) that account for 4.7%–7.2% of meningiomas and that are associated with a 29%–52% post-resection recurrence rate [4]. Moreover, they exhibit a tendency for malignant progression with a significant increase in tumor cell migration and infiltration of surrounding tissues [5]. The anaplastic variant (grade III) is exceedingly rare, accounting for 1%–3% of all meningiomas [6]. The anaplastic histology observed in these tumors associates to poor prognosis with median overall survival of 1.5 years [7], with 5-year survival ranging from 47% to 61% [8–11].

Past studies have shown that the risk of meningiomas recurrence is strongly correlated with the molecular profile of the tumor [12]. Genomic instability is one of the key differentiators between grade I and grade II–III meningiomas [13].

The bi-allelic mutation or loss of the tumor suppressor gene neurofibromatosis 2 (*NF2*) on chromosome 22, is found in approximately 50% of sporadic meningiomas [14–17]. Recent studies employing next generation sequencing methodology have detected new driver mutations in meningiomas, including *TRAF7*, *KLF4*, *AKT1*, SMO, *PIK3CA*, *NOTCH2*, *SMARCB1*, *CHEK2*, *SMARCE1* and *POLR2A*, particularly in the remaining half of meningiomas with wild-type *NF2* [17–19].

Extensive whole-exome or whole-genome sequencing has provided a large body of information about the mutational landscape of meningiomas [16,17,19–21]. Four distinct meningioma mutational subgroups have been proposed, defined by mutations in *NF2*, *TRAF7*, the hedgehog pathway or *POLR2A*. However, such a stratification of

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https://doi.org/10.1016/j.clineuro.2018.12.004
Received 29 September 2018; Received in revised form 16 November 2018; Accepted 6 December 2018
Available online 07 December 2018
0303-8467/

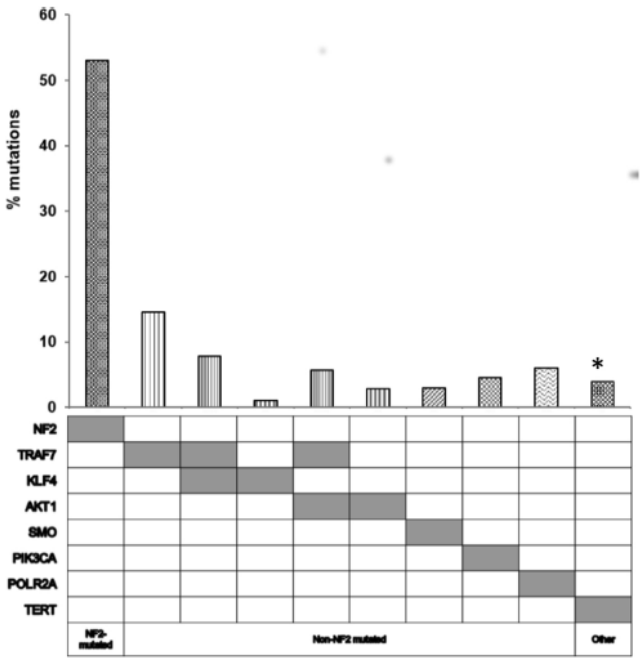

Fig. 1. Frequency of the most common genetic alterations found in meningiomas according to independent studies (17, 18, 20, 39, 41, 51,58, 60, 64, 67). Meningiomas are divided into *NF2*-mutated meningiomas *(NF2* alterations which include *NF2* loss and/or *NF2* mutations) and non-*NF2*-mutated meningiomas. The latter group present *TRAF7* mutations alone or in combination with *KLF4* or *AKT1* mutations, *SMO*, *PI3KCA* and *POLR2 A* (17). Additionally, the occurrence of *TERT* promoter mutations (*) are independent to other mutations, and they are more prevalent in more malignant meningiomas, being, therefore, a prognostic predictor (68, 69).

meningiomas based on mutational analysis alone has been proven not to satisfy the clinical need for distinction between patients who need (or do not need) an adjuvant treatment [17].

2. *NF2*-mutated meningiomas

Abnormalities in the 22q locus have been identified as the most frequent finding in meningiomas, and mutation, allelic inactivation or loss of the tumor suppressor *NF2* [15–17] have been described in approximately half of sporadic meningiomas [22–25] (Fig. 1). Based on this observation, it has been suggested that *NF2* might play a central role in regulating leptomeningeal cell proliferation [26]. Bi-allelic inactivation of the *NF2* gene leads to the loss of its product, merlin, also known as schwannomin [15]. And, *NF2* inactivation is thought to be an early event in sporadic meningiomas pathogenesis, frequently observed in grade I tumors, but also in high-grade tumors [7].

Alterations in the merlin protein have been associated with cell shape, particularly with mesenchymal-like cell phenotypes rather than epithelioid-like ones. Decreased *NF2* expression was observed in up to 80% of transitional or fibroblastic subtypes [27,28], while it was observed in only 28.5% of meningothelial meningiomas, which typically occur at the anterior skull base [29]. Kros et al. [30] analyzed 42 cases of sporadic meningiomas for LOH, karyotyping and fluorescence in situ hybridization, and they have demonstrated a significant correlation between tumor localization at the anterior skull base and an intact chromosome 22q, corroborating the paucity of *NF2* alteration in meningiomas on this site and in megingothelial subtype, the prevalent histological subtype in this site [31].

Although familial meningiomas are uncommon, they are usually associated with *NF2* alteration [32,33].

3. Non-*NF2* mutated meningiomas

Recent genomic analyses have shown that *KLF4*, *TRAF7*, *SMARCE1*, *POLR2 A*, telomerase reverse transcriptase (*TERT*), and *AKT1*, *SMO* are commonly mutated in non-*NF2* mutant meningiomas [16,17,20,34].

3.1. *KLF4* mutations

The *KLF4* gene, located on chromosome 9q31, belongs to a family of 17 members, all containing three C2H2 zinc finger motifs in the C-terminal region [35]. *KLF4* is linked to transcriptional activation and repression, including oncogenic activation and tumor suppression in a context-dependent manner [35,36]. *KLF4*, together with *OCT3/4*, *SOX2* and *c-MYC*, is one of the key genes necessary for the reprogramming of mouse fibroblasts into induced pluripotent stem cells (iPS) [37], indicating its role in stem-cell maintenance (57). *KLF4* mutations in meningiomas are all the same: the missense mutation c.1225 A > c, p.K409D located in the lysine residue at the first of three amino acids of the zinc finger, which makes physical contact with DNA, and is therefore central to DNA binding and highly conserved in evolution [38]. Approximately 9% of meningiomas present with this $KLF4^{K409Q}$ mutation, although it is more prevalent in grade I meningiomas [39]. This mutation was also identified in secretory meningiomas. In contrast, *KLF4* was downregulated in anaplastic meningiomas compared to benign secretory meningiomas, which lead to a decrease of its tumor suppressor role with dysregulation of cell cycle, apoptosis and invasion [40]. Cytokeratins 4 and 19 are clinical hallmarks of secretory meningiomas, and they are regulatory targets of *KLF4* [41]. This interaction may be linked to the presence of cytokeratin-positive globules unique to meningiomas of the secretory variant. In particular, the *KLF4* mutation has also been observed in secretory meningiomas associated with glial tumors, in two different patients with a glioblastoma and an anaplastic astrocytoma [42].

The *KLF4* mutation has also been described in an intraductal papillary mucinous neoplasm of the pancreas [43]. Additionally, in kidney cells, KLF4 co-regulates the bradykinin B2 receptor [44].

3.2. TRAF7 mutations

Tumor necrosis factor receptor associated factors (TRAFs) transduce the cellular effects mediated by TNF family ligands by their ability to couple TNF receptor family proteins to signaling pathways. Functionally, TRAF proteins are involved in innate and adaptive humoral immune responses acting both as cytoplasmic regulatory molecules and as signal transducers for receptors [45]. The RING finger domains of TRAF-2, -6 and -7 activate their downstream pathways by promoting ubiquitination events [46,47]. The function of TRAF7 is still not completely elucidated. However, interaction between TRAF7 and MEKK3 has been described, with enhancement of MEKK3-mediated signaling [46,48]. It was also described that TRAF7 binds to c-Myb and inhibits its transactivation by sumoylation [49]. Finally, it has been shown that TRAF7 is linked Toll-like receptor 2 stimulation which leads to NFκB transcription factor activation [50].

Mutations in *TRAF7*, located on chromosome 16p13.3, are observed in 14.5–20% of meningiomas [39,51]. Serpin2 A [52], matrix metallopeptidase 2 [53], IGFBP4 and IGFBP7 [54,55], which are direct targets of NFκB, are up-regulated in TRAF7-deficient cells. TRAF7 influences signal transduction in several ways. TRAF7 interacts with MEKK3/MAP3K3 through its WD40 domains [56], and NF-κB via its coiled-coil domain, modulating its ubiquitination. The RelA/p65 member of the NF-κB family is also ubiquitinated by TRAF7, and in both cases, TRAF7 promotes Lys-29-linked polyubiquitination [45]. Moreover, down-regulation of stress-related genes ceramide synthase 2, the ubiquitin-binding protein p62 (*SQSMT1*) and the apoptosis-related gene serglycin (*SRGN*), were observed in TRAF7-deficient cells [57].

TRAF7 mutations are highly specific for meningiomas, and they are confined to exons 13–20 coding for the seven WD40 domains in the C-terminal portion (17,51).

Nearly all cases of secretory meningioma (97%) harbor mutations in both *TRAF7* and *KLF4* K^{409Q} but lack mutations in *NF2* [20]. The *TRAF7* mutation is also found in other meningioma subtypes [17]. Interestingly, cumulative observation proved that these *KLF4* and *TRAF7* mutations were both mutually exclusive with the *NF2* alteration [51]

3.3. AKT1 mutations

AKT1, located on chromosome 14q32, is mutated recurrently in meningioma, producing a known oncogenic alteration of glutamic acid to lysine at codon 17 (c.49 G > A, p.E17 K), and has been reported exclusively as not overlapping the *NF2*, *KLF4* and *SMO* mutations [17]. This mutation is commonly observed in meningothelial meningiomas but is rarely reported in meningiomas of higher grades [58]. A majority of meningiomas with *TRAF7* mutations also harbor mutations in *KLF4*, as described above, or in *AKT1* (6.8–9% of meningiomas), but not in both genes [17,20,51]. The $AKT1^{E17K}$ mutation activates constitutively PI3K/AKT/mTOR oncogenic signaling pathway [59]. Moreover, the presence of the $AKT1^{E17K}$ mutation in skull-base meningiomas have been associated with reduced time of recurrence [60].

3.4. POLR2A mutations

RNA polymerase II subunit A gene (*POLR2 A*), located on chromosome 17p13.1, encodes the largest subunit of RNA polymerase II, the polymerase responsible for synthesizing messenger RNA. The product of this gene contains a carboxy terminal domain composed of heptapeptide repeats that are essential for polymerase activity. Mutations in *POLR2 A* were discovered by searching for somatic mutation in meningiomas that lacked known mutation in classical driver genes described previously (18). Two different mutations at exon 7 (c.1207C > A, p.G403 K or c.1310_1315delACCTTC, p.L438_H439del) were present in 6% of benign meningiomas. *POLR2 A* exon 7encodes the highly conserved catalytic subunit of RNA polymerase II, responsible for interaction with TFIIB during the formation of the pre-initiation complex [61]. These alterations were confirmed as being somatic, exclusive to grade I meningiomas and mutually exclusive with previously established driver genes [17].

3.5. TERT mutations

Telomerase reverse transcriptase gene (*TERT*), located on chromosome 5p15.33, presents reverse transcriptase activity, that maintains telomere ends by adding the TTAGGG telomere repeat. TERT activation has been demonstrated in 10% of grade I, 50% of grade II and 95% of grade III meningiomas. Interestingly, *TERT* promoter mutations (g.228C > T and g.250C > T) are associated with recurrent meningiomas, and the highest frequency of such mutations (28%) are present in recurrent meningiomas with histologic progression [62]. Therefore, *TERT* promoter mutation is predictive of progression [63] and a shorter recurrence-free survival, especially in recurrent higher grade meningiomas [64,65].

4. Epigenetic alterations

4.1. DNA methylation

Patients with WHO grade I meningiomas who were molecularly assigned to an intermediate methylation class (WHO grade I MC int) had a less favorable clinical course than did patients with WHO grade I meningiomas diagnosed solely based on histology. In fact, the outcome of these patients (WHO grade I MC int) was indistinguishable from that of patients with WHO grade II meningiomas. Similarly, patients with WHO grade II meningiomas that were molecularly assigned to a benign methylation class (WHO grade II MC ben) had a better outcome than the average outcome of patients with histologically defined WHO grade II meningiomas. Consequently, the stratification for the methylation class has been demonstrated to be of higher value for the prediction of progression-free survival than WHO grading. The described combinatorial methylation classes have delineated subgroups with distinct prognoses within all WHO grades, showing the benefit of methylation class-based grading and, therefore, potentially reduce under or over-treatment in meningioma patients [51]. In addition, it has been demonstrated that the hypermethylation of the *SFRP1* promoter could be a mechanism of gene inactivation in meningiomas [66]. Moreover hypermethylation of *p73, TIMP3, GSTP1, MEG3, HOXA6, HOXA9, PENK, WNK2* and *UPK3A* have been recently described associated either to tumor progression/malignant transformation or tumor recurrence [67].

4.2. SWI/SNF complex mutations

The switch/sucrose non-fermentable (SWI/SNF) family is an ATP-dependent chromatin-remodeling complex involved in epigenetic regulation in human [68,69]. The catalytic activity of this complex disrupts DNA-nucleosome contacts, moves nucleosomes along DNA and ejects or exchanges nucleosomes, enabling DNA accessibility by opening the chromatin and consequently allowing an active transcription. This complex, also called the Brg-/Brama-associated factor, is a large multimeric assembly of 10–15 subunits. Each SWI/SNF complex contains one of two mutually exclusive catalytic ATPase subunits (either SMARCA2 or SMARCA4), a set of highly conserved core subunits (SMARCB1, SMARCC1 and SMARCC2) and variant subunits, including SMARCE1. Interestingly, heterozygous germline mutations in the *SMARCE1* gene, located on chromosome 17q21.2, were reported in 16 patients from 11 unrelated families with spinal and intracranial clear-cell meningiomas. These mutations were characterized as loss-of-function mutations, including frameshift and nonsense mutations, as well as an inversion and two large deletions. All symptomatic males with a *SMARCE1* mutation developed meningiomas in childhood (age range 2–10 years), while the symptomatic carrier females developed tumors somewhat later in adolescence or early adulthood (age range 14–30 s)

[18,34,70,71]. *SMARCE1* mutations is frequent in spinal cord meningiomas with clear cell histology [18,34,72].Germline mutations in *SMARCB1* have also been reported in three families with both multiple schwannomas and meningiomas [73–77]. Additionally, *SMARCB1* mutations have been reported to cause malignant rhabdoid tumors and schwannomatosis. However, screening for the *SMARCB1* germline mutation on individuals and families with multiple and isolated meningiomas suggested that such mutations are not prevalent in multiple meningiomas [78,79]. Interestingly, *SMARCB1* is located on chromosome 22 in close proximity to *NF2*, and co-occurrence of recurrent *SMARCB1* mutations in NF2-mutated meningiomas has also been described [19].

The importance of the SWI/SNF complex in tumorigenesis has been further reinforced by the detection of somatic mutations in the *ARID1A* and *PBRM1* subunits of SWI/SNF complex, and as major cancer-driving gene mutations in ovarian and renal clear-cell tumor subtypes, respectively [80,81].

4.3. Histone modifications

Another major epigenetic determinant for gene expression and cellular differentiation is the histone modification through methylation and acetylation [82]. Particularly modifications of lysine 27 (K27) of histone H3 play a crucial role in tumorigenesis [83]. Methylation of H3K27 is regulated by the EZH2 subunit of the PRC2 complex [84–86] and trimethylated H3K27 (H3K27me3) is associated to gene silencing [87]. Dysregulation of H3K27 methylation has been identified in several different cancers, including breast, prostate, colon, ovarian cancers, and malignant peripheral nerve sheath tumors [83,88–92]. In meningiomas, H3K27 dysregulation has been described in *AKT1* and *NF2* mutated meningiomas, where complete loss of its trimethylation has been associated to worse outcome, but not an obligatory finding among high-grade meningiomas (17). Immunohistochemical evaluation of H3K27me3 was reported as an useful adjunct tool for determining meningioma grade, particularly for WHO grade II and meningiomas with histological borderline diagnosis of WHO grade I and II.

4.4. Chromosomal copy number variations

Small recurrent regional amplifications on chromosome 6p21-p22, 16p13, 13q33, 17 and 19 have been described (94).

4.5. Micro-RNA

Cumulative evidences suggest miRNAs, a member of the non-coding endogenous RNA region of approximately 22 nucleotides [93] play an important role in a number of biological processes including metastasis, proliferation, apoptosis, stress resistance, tumorigenesis, and cellular differentiation [94–96].miRNA-224 was associated to malignant progression of meningioma (100).

Despite the previously demonstrated association between miRNA expression and a variety of other cancers, Katar, et al [94], examined the association between meningioma and miRNA-21, miRNA-107, miRNA-137 and miRNA-29b expression. Of the four different miRNA types, only miRNA-21 expression showed a significant increase in grade 2 and 3 lesions as compared to grade 1 lesions, and miRNA-107 expression was significantly lower in grade 2 and 3 lesions vs. Grade 1 lesions, while miRNA-137 and miRNA-29 b expression exhibited a statistically nonsignificant decrease in grade 2 and 3 lesions as compared to grade 1 tumors. In this study, despite a decrease in miRNA-137 with increasing disease grade, this difference was not significant, probably due to low sample size.

Saydam et al. [97], examining the association between different types of miRNA and meningioma. They found an increase in miR-335, miR-98, and miR-181a, while miRNA-200a, miRNA-373, and miRNA-575 decreased. Also, in their laboratory study, miRNA-200a inhibited the growth of meningioma in the culture medium. In another study, Wang, [98], et al, identified that, miR-224 expression could predict the overall survival and recurrence free survival of patients with meningioma and it might be a promising therapeutic target for treating malignant meningiomas.

5. Molecular signaling pathways

5.1. WNT

The Wnt pathway is one of the important signaling pathways reported as being dysregulated in meningiomas [99–102]. The activation of Wnt signaling pathway leads to the increase of β-catenin cytosolic levels. This occurs through the binding of Dishevelled (DVL) proteins to AXIN, and translocation to the cell membrane, forming a large molecular complex consisting of Wnt-Fz-LRP5/6-DVL-AXIN. This complex is destroyed when AXIN is pulled out, and then β-catenin can no longer be degraded [103]. The gene that codes for one of the Wnt receptors, Frizzled class receptor 2 (*FZD2*), was reported as differentially expressed in meningiomas compared to non-malignant leptomeningeal cells, being 3.7 fold higher in the tumor [104]. Moreover, genes coding for key molecules of this pathway, namely APC and E-cadherin (*CDH1*), and AXIN, have been reported as having loss of heterozigozity (LOH) and their products as downregulated in meningiomas [105–107], reinforcing the importance of this molecular signaling pathway in these tumors.

5.2. Sonic hedgehog

The smoothened, frizzled class receptor gene (*SMO*) encodes for the smoothened homologue, a member of the Sonic Hedgehog signaling (SHH) pathway, involved in both embryogenesis and several key cellular processes, including proliferation and angiogenesis. *SMO*, located at 7q32.1, interacts with suppressor of fused homologue (SUFU), which translocates the zinc-finger protein GLI1 to the nucleus, subsequently activating target genes [108]. The SMO-mutant is described with a frequency between 3% and 5% of all meningiomas showed 2 recurrent variants, c.1234C > T, p.L412 F (70%) and c.1604 G > T, p.W535 L (15%), and a highly recurrent phenotype of grade I meningothelial lesions arising from the anterior medial skull base [19,39]. The strong association of the *SMO* mutation with meningiomas of the anterior skull base location might be related to the central role of the SHH pathway in the development of the ventral forebrain and median craniofacial skeleton [109,110]. The *SMO* mutations rarely co-occur with mutations of *NF2* or *TRAF7* mutations or with chromosome 22 loss [12]. Germline mutations in *SUFU*, a negative regulator of the SHH signaling pathway, have also been reported in meningiomas (9,10).

5.3. PI3K/AKT/mTOR

The PI3K-AKT-mTOR signaling pathway is another important growth-favoring pathway, particularly associated in a subset of meningiomas harboring PI3K mutations [111]. Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene (*PIK3CA*) is located at 3q26.32 and encodes the phosphoinositide-3-kinase (PI3K) catalytic subunit p110a.Five different well-established oncogenic mutations (E110del, N345 K, E453 K, E545 K and H1047R) in *PIK3CA* have been described (111).

This subset of meningiomas lacked mutations in *NF2*, *AKT1* and *SMO*, but they tended to present *TRAF7* mutations, being meningothelial or transitional subtypes, preferentially localized at the skull-base (64). Another gene in this signaling pathway, *AKT1* is located on chromosome 14q32, and is mutated recurrently in meningioma, producing a known oncogenic alteration of glutamic acid to lysine at codon 17 (c.49 G > A, p.E17 K). And, this mutation has been reported exclusively as not overlapping the *NF2*, *KLF4* and *SMO* mutations [17].

This mutation is commonly observed in meningothelial meningiomas but is rarely reported in meningiomas of higher grades [58]. A majority of meningiomas with *TRAF7* mutations also harbor mutations in *KLF4*, as described above, or in *AKT1* (6.8–9% of meningiomas), but not in both genes [17,20,51]. The $AKT1^{E17K}$ mutation activates constitutively PI3K/AKT/mTOR oncogenic signaling pathway [59]. Moreover, the presence of the $AKT1^{E17K}$ mutation in skull-base meningiomas have been associated with reduced time of recurrence [60]

6. Angiogenesis and anothers ways

Meningiomas are highly vascular tumors, and therefore signaling pathways related to angiogenesis have been studied in these tumors. The cytokine vascular endothelial growth factor (VEGF) was originally described as a vascular permeability factor and as a positive regulator of angiogenesis by promoting the migration, proliferation and tube formation of endothelial cells [112]. VEGF up-regulation was demonstrated in meningiomas, suggesting its role as a pro-angiogenic factor [113–116]. Nonetheless, despite the higher vascularity in higher-grade meningiomas, any parallel increase of VEGF expression was found in atypical or anaplastic meningiomas [117,118]. Additionally, the predictive power of tumor recurrence of the ratio between the pro-angiogenic factor as VEGF and the anti-angiogenic factor as SEMASA, associated with low microvessel density, has been controversial [119]. Remodeling the extracellular matrix (ECM) is relevant for angiogenesis, and metalloproteinases (MMPs) have been widely implicated as mediators of angiogenesis, and also as playing a role in the degradation of the ECM facilitating tumor invasion. Additionally, MMPs regulate cell adhesion, control apoptosis through the release of death or survival factors and regulate the bioavailability and/or activity of growth factors by mediating receptor turnover or by cleaving matrix proteins associated with growth factors [120]. In this scenario, the ability of MMP9 to trigger the release of VEGF, which regulates angiogenesis and vascular permeability, as mentioned [121] is well documented. Upregulation of MMP9 has been related to an increase in intratumoral vascular density, tumor invasion and recurrence and peritumoral edema [122], being pointed out as a predictive factor for tumor recurrences, especially for benign meningiomas [123]. Indeed, for these reasons, associated with controversial results in the literature, we chose to study these markers more thoroughly, in order to find a relationship between these markers and the malignization of these tumors. In our cohort [124,125] we found differential expression of *MMP9* among meningiomas; however its expression was higher among the atypical meningiomas presenting recurrence (Fig. 2B); and no differential expression was observed among distinct grades of meningiomas (Fig. 2A).

Hyaluronic acid is an important component of the brain ECM, known to be a permissive substrate for cell migration in tumor progression [126]. The expression level of CD44, a hyaluronic acid receptor, was found in 71% of benign, 83% of atypical and 100% of anaplastic meningiomas. However, similarly to the MMP9 expression profile, no correlation of its expression level and tumor grade was observed [127]. The loss of the TGF inhibitory effect has also been described in higher-grade meningiomas and in combined alterations of WNT and p53-signaling pathways [128].

The next-generation sequencing approaches have established a somatic mutational profile of meningiomas. However, the mutational status alone or combined to histological subtype and tumor localization have not provided prognostic or therapeutic guidance [129], and additional molecular predictive markers are needed.

7. Discussion

The study of meningioma is undergoing a renaissance due to the application of multiplatform molecular, genomic, and epigenetic profiling. These large-scale, systematic approaches inform a molecular taxonomy that promises to influence diagnosis, disease classification, and, ultimately, clinical management.

Actually, the current WHO classification of the central nervous system (2016), combined histological-molecular classification termed integrated diagnosis is applied for the diagnosis of gliomas [2] because genotype is more significantly associated with prognosis than histology [130]. However, as described above, more detailed investigations about the correlation between genotype and prognosis are required to establish integrated diagnosis for meningioma. In meningioma, few surrogate markers for mutations were reported. Sahm et al. [58] described the strong up-regulation of SFRP1 expression in all meningiomas with AKT1 E17 K. Brastianos et al. [16] demonstrated the strong immunoreactivity for GAB1 in meningiomas harboring SMO mutations, and STMN1 expression was observed in AKT1-mutated and SMO-mutated meningiomas [16]. However, the sensitivity, specificity, and accuracy of the immunohistochemistry for genotyping of meningiomas remain unclear.

As described by Linda, et al, [131] further understanding of the factors that drive meningioma development and progression will lead to the classification of every patient's tumor according to its signature alterations, ushering in an era in which meningiomas will be considered in the same light as other tumors whose molecular underpinnings have fueled the nascent precision medicine age.

8. Conclusion

Combined analysis of exome, transcriptome, methylome and future approaches for epigenetic aspects in meningiomas may allow researchers to unveil a more comprehensive understanding of tumor progression mechanisms and, consequently, a more personalized clinical approach for patients with meningioma.

Disclosure

The authors have no personal financial or institutional interest in

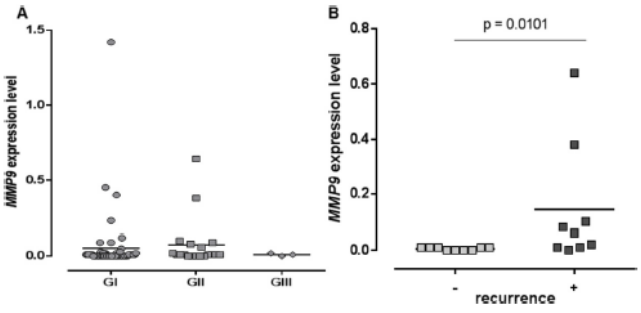

Fig. 2. *MMP9* expression profiles in meningiomas according to WHO grade classification. (A) *MMP9* transcript levels were determined by quantitative real-time PCR in 57 grade I meningiomas (GI), 18 grade II meningiomas (GII) and 3 grade III meningiomas (GIII) according to previous work (105, 106). The relative expression values were calculated according to $2^{-\Delta Ct}$, where ΔCt = Ct specific gene- geometric mean Ct of housekeeping genes the *HPRT* and *GUSB* expression levels for each sample of meningioma. The horizontal bars show the mean *MMP9* expression of each group: GI = 0.050; GII = 0.075; AGII = 0.010. (**A**) The *MMP9* expressions among the groups was not statistically significant ($p > 0.05$, Kruskal Wallis test). However, *MMP9* expression levels according to recurrence (+) or no recurrence (-) in grade II meningiomas were significantly different (p = 0.0101, Kruskal Wallis test), as in (**B**).

any of the drugs, materials, or devices described in this article.

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Análise crítica

O estudo do meningioma está passando por um renascimento devido à aplicação multiplataforma de sequenciamento em larga escala para a determinação de perfis moleculares, genômicos e epigenéticos. Essas abordagens sistemáticas em larga escala têm permitido uma taxonomia molecular que promete influenciar o diagnóstico, a classificação da doença e, finalmente, o manejo clínico.

Na verdade, a atual classificação da OMS do sistema nervoso central (2016), aplica uma classificação histológico-molecular combinada, denominado diagnóstico integrado, atualmente aplicado para o diagnóstico de gliomas (3). Esta prática tem demonstrado que o genótipo está mais associado ao prognóstico do que a histologia (139). No entanto, os esforços para estabelecer a correlação entre genótipo e prognóstico para os meningiomas estão apenas se iniciando e são necessárias investigações mais detalhadas para a determinação de um diagnóstico integrado para este tipo de tumor. No meningioma, observa-se uma paucidade de mutações somáticas associadas ao fenótipo tumoral. Entre estas, Sahm et al. (27) descreveram a forte regulação positiva da expressão de *secreted frizzled related protein 1* (*SFRP1)* em todos os meningiomas com mutação no gene *AKT serine/threonine kinase 1* (*AKT1*)^{E17K}. Brastianos et al. (140) demonstraram imunorreatividade para a proteína *GRB2 associated binding protein 1* (GAB1) em meningiomas com mutação no gene *small ubiquitin-related modifier* (*SUMO)* e para a proteína *stathmin1* (STMN1) em meningiomas com mutações em *AKT1* e *SUMO*. No entanto, apesar dos achados nestes estudos, a sensibilidade e especificidade da imuno-histoquímica para correlação com a genotipagem em meningiomas permanecem incertas.

Conforme descrito por Linda et al. (141), uma maior compreensão dos fatores que impulsionam o desenvolvimento e a progressão do meningioma permitirá a classificação do tumor de acordo com suas alterações de assinatura molecular, iniciando uma era em que os pacientes com meningiomas também receberão tratamentos personalizados dentro da concepção da medicina de precisão.

Identificação dos marcadores implicados na recorrência dos meningiomas

PUBLICAÇÃO 9

Título	**A metabolic and extracellular matrix remodeling transcriptional signature impacts tumor progression in meningioma**		
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Revista	The Lancet Oncology		
Submetido	23/01/2021	**Aceito**	
Citação completa			
Fator de Impacto	33.752		
Citações	Scopus: Web of Science: ; Google scholar:		

A metabolic and extracellular matrix remodeling transcriptional signature impacts tumor progression in meningioma

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Abstract

Purpose: In this study, we searched for genetic signatures associated to tumor progression and recurrence in our cohort of meningiomas combining the analysis of targeted exome, transcriptome and protein expression.

Methods: We enrolled 91 patients submitted to surgical of intracranial meningioma in our institution between June 2000 to November 2007. The search of somatic mutations was performed by NGS through a customized panel, and MLPA for *NF2*-LOH. The transcriptomic profile was analyzed by QuantSeq 3´mRNA-Seq. The differentially expressed genes of interest were validated at the protein level by immunohistochemistry. The molecular results were correlated to the clinical parameters, particular to tumor recurrence and a gene set predictive of clinical outcome was identified by Samr analysis.

Results: In this meningioma cohort of 67 grade I, 18 grade II and 6 grade III and follow up time of 101 ± 47 months, tumor recurrence was observed in 26% and death in 22% of cases. The transcriptomic analysis identified upregulated set of genes related to metabolism and cell cycle, and downregulated genes related to immune response and extracellular matrix remodeling in grade II (atypic) meningiomas, with significant difference in recurrent compared to non-recurrent cases. EZH2 nuclear positivity associated to grade II, particularly to recurrent tumors.

Conclusion: the transcriptomic analysis of our meningioma cohort identified set of differentially expressed genes in grade II related to activation of oxidative metabolism, cell division, cell motility due to extracellular remodeling and to immune evasion. Among them, the genes related to cell cycle and extracellular remodeling were predictive of clinical outcome, and may be targets for adjuvant therapeutic strategies.

CONTEXT

Key Objective This study sought to provide contemporary data from a institutional of comprehensive cancer centers with respect to genetic signatures associated to tumor progression and recurrence in our cohort of meningiomas combining the analysis of targeted exome, transcriptome and protein expression.

Knowledge Generated: personal management is necessary to the best neuro-oncological management of meningiomas.

Relevance Current data support that combined analysis of exome, transcriptome, methylome and future approaches for epigenetic aspects in meningiomas may allow researchers to unveil a more comprehensive understanding of tumor progression mechanisms and, consequently, a more personalized clinical approach for patients with meningioma.

INTRODUCTION

Meningiomas, tumors that originate from meningothelial cells, account for approximately 30% of all new diagnoses for central nervous system neoplasms[1], and in the 2016 WHO classification[2], they are divided into three grades: I (GI), II (GII), and III (GIII). Grade I meningiomas are typical or benign tumors, stratified into nine histological subtypes: meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lympho-plasmacyte-rich, and metaplastic. They represent 88–94%, of all meningiomas [3]. Atypical meningiomas are "intermediate grade" malignancies (GII) that account for 4.7%–7.2% of meningiomas and are associated with a 29%–52% post-resection recurrence rate [4]. Moreover, they exhibit a tendency for malignant progression with a significant increase in tumor cell migration and infiltration of surrounding tissues [5]. The anaplastic variant (GIII) is exceedingly rare, accounting for 1%–3% of all meningiomas, associated with poor prognosis and a median overall survival of 1.5 years [6], and 5-year survival ranging from 47% to 61%[7].

Total tumor resection provides the best chance for long-term survival of patients with GII and GIII meningiomas, but such a procedure should be carefully weighed to ensure that it does not increase morbidities or complications due to therapeutic procedures[8]. Radiotherapy is still a controversial issue. Although positive impact has been

shown when tumor recurrence and progression-free survival were analyzed[9], controversial results were reported concerning tumor recurrence among GII meningiomas[10].

The application of multiplatform molecular, genomic, and epigenetic profiling has introduced molecular stratification with a correlation to clinical outcome. This application has guided therapeutic strategies. In this study, we searched for genetic signatures associated with tumor progression and recurrence in our cohort of meningiomas, combining the analysis of targeted exome, transcriptome and protein expression.

METHODS

Tumor samples and clinical data

We enrolled 91 patients submitted for surgery of intracranial meningioma in our institution between June 2000 and November 2007. The inclusion criteria were as follows: 1) newly diagnosed meningioma; 2) frozen tumor sample available; and 3) surgical resection of > 80% of the tumor bulk. Exclusion criteria included: 1) prior history of treatment, either surgery or brain irradiation, and 2) age < 18 years. The study was conducted in accordance with institutional ethical guidelines (research protocol 200/05). Histopathological stratification was performed according to the WHO grading system[2].

Sample Preparation

Tumor fragments were immediately snap-frozen in liquid nitrogen upon surgical removal. They were cryosectioned, stained for hematoxylin-eosin, and hemorrhagic areas were microdissected prior to DNA and RNA extraction using an AllPrep DNA/RNA Mini Kit (Qiagen, Hilden, Germany)[11,12]. Blood DNA was extracted using Qiagen Blood DNA Mini Kit. RNA integrity was determined by the TapeStation 2200 system (Agilent Technologies, Carlsbad, CA).

Mutational profile

The mutational profile was determined through a customized panel targeting *NF2*, *KLF4*, *TRFA7*, *AKT1*, *SMO*, *PIK3CA*, *POLR2A*, *SUFU*, *SMARCB1*, *SMARCE1*, and *TERT*.. Variants were called using *freebayes* with the *–pooled-continuous* and *–pooled-discrete* flags activated. Only variants with a minor allele fraction >10% were considered for downstream analysis. Annotation of the variants was performed with *annovar, as described previously*[13]. We selected candidate somatic variants according to the following criteria: 1. Known somatic hotspot or 2. Absent in publicly available population databases, including 1000 Genomes, gnomAD, and the local database SELAdb[14]. We used *CONTRA*[15] to perform a copy-number variation (CNV) analysis. Reference samples derived from normal blood DNA were used to generate the baseline copy-number profile.

Multiplex ligation-dependent probe amplification (MLPA)

NF2 loss of heterozygosity was determined through MLPA screening using the commercial kit SALSA MLPA probemix P044-NF2 (RC-Holland, Amsterdam, the Netherlands), with 200ng of tumor DNA and blood controls. PCR products were analyzed on an ABI 3130XL sequencer (Applied Biosystems, Foster City, CA).

Transcriptome analysis

The transcriptomic profile was analyzed using RNASeq. Libraries were prepared using a QuantSeq 3'mRNA-Seq Library Prep Kit-FWD (Lexogen, Vienna, Austria) with 1 µg of tumor RNA. The library concentration was measured by Qubit Fluorometer and Qubit dsDNA HS Assay Kit (Applied Biosystems), and the size distribution was determined using an Agilent D1000 ScreenTape System (Agilent Technologies). Unsupervised clustering (consensus cluster analysis) was performed with *ConsensusClusterPlus*[16]. To identify clusters of genes that defined the four groups of tumors identified by consensus cluster, we first used the *topTableF* function from *limma* to filter out genes that were not differentially expressed. We then used *pheatmap* to perform hierarchical clustering analysis with complete clustering and Pearson's correlation as the distance metrics. Pathway analysis and gene set enrichment analysis were performed using online tools such as GSEA (http://software.broadinstitute.org/gsea) and WebGestalt (http://www.webgestalt.org/). To identify genes whose expression levels were predictive of overall survival (OS) and disease-free survival (DFS), we used the *SAM* function from

the R/CRAN *samr*[17] package. The counts per million reads mapped (CPM) were log transformed and normalized to z-score for visualization in heatmaps.

Tissue Microarray (TMA)

TMA was built by spotting three regions of interest containing tumor tissue of 1.0mm. In total, 55 meningioma cases were represented.

Immunohistochemistry

The protein expression level for EZH2, PCG1α, CD11B, HLA-E, COX5A and H6PD were analyzed by immunohistochemistry using a Novolink Polymer Detection Systems kit (Leica Biosystems, Wetzlar, Germany). The reaction was developed using a DAB solution, and nuclei were counterstained with Harris hematoxylin. The percentage of positive nuclei for EZH2 was quantified in five random fields at 400x magnification, and cytoplasmic positivity was analyzed by color deconvolution in Image J/Fiji[18].

Statistical analysis

Data distribution was tested using the Kolmogorov-Smirnov test. Expression levels in different grades and in different subtypes of grade I meningiomas were investigated using non-parametric Kruskal-Wallis´ and post-hoc Dunn´s tests. Correlation between relative gene expression values was assessed using the non-parametric Spearman-rho correlation test, and the results were plotted using the corrplot package in R. Discrimination of variables was calculated by the receiver operator characteristic (ROC) curve utilizing area under curve and asymptotic significance. Differences were considered statistically significant when $p<0.05$. The analyses were performed in the SPSS for Windows, version 21.0 (IBM Corporation, Armonk).

RESULTS

Demographic and Clinical characteristics

We analyzed 91 meningioma patients (62 females/29 males; 2.13:1.0 ratio) with ages ranging from 27 to 80 years old (54.8 ± 13.7yo), followed for 101 ± 47 months. Of these, 67 cases were GI, being 21 meningothelial-M, 36 transitional-T, 10 fibrous-F), 18 GII and 6 GIII. Tumor recurrence was observed in 24 cases (13 GI, 11 GII) within a time interval ranging from 24 to 104 months (63 ± 41 months). In total, 20 deaths were observed (7 GI, 7 GII and 6 GIII), and among these, 4 deaths were related to surgical complications (STable1).

Somatic mutations

NF2 deletions were determined by NGS analysis and confirmed by MLPA analysis. NF2 alterations were detected in 49 cases. Of these, 3 were homozigous deletions; 8 were heterozigous deletions combined with nonsense mutations; 4 were missense mutations; 15 showed small rearrangements, while in 18 cases no mutation was detected in the second allele. They were distributed in 29 GI (3M, 18T, 8F), 18 GII, and 2 GIII. Additionally, 18 mutations were detected in 5 *TRAF7*, 4 *SUMO*, 3 *AKT*, 3 *KFL4*, 2 *TERT*, and 1 *SUFU*, distributed in 9T, 4M, 2F, 2GII e 1GIII. No mutations were found in *PI3KCA*, *POLR2* and *SMARCB1* (STable 2).

Transcriptomic analysis

The RNASeq yielded a mean of 4.1 million filtered reads, detected 14,437±1,350 genes, and among these 13,085 presented ensemble gene ID. An unsupervised clusterization identified four clusters with 175, 196, 137, and 489 genes. (Fig.1A). In order to predict possible functions of the surrogate genes in each cluster, we performed enrichment analysis of the Biological Processes of the Gene Ontology (GOBP) (Fig.1B, STable3).

Cluster 1 comprised 175 genes significantly enriched for the ATP metabolic process and oxidative phosphorylation (OXPHOS). Twenty genes related to OXPHOS, 8 to glycolysis, 5 to TCA cycle and 3 to glutaminolysis were upregulated in GII compared to GI. In contrast, *H6PD* and *PGD* of the pentose phosphate pathway were downregulated,

and negatively correlated with OXOPHOS gene expressions (Fig.2A, SFig.3). Interestingly, GII meningiomas presented upregulation of the *ESRRA* and *PPARGC1A* (Fig.2B), whose expressions were significantly correlated to metabolic gene expressions. In particular, *ESRRA* connectivity was reinforced in GII (Fig.2C, STable5). Of note, the majority of these metabolic genes (36 out of 44) were significantly higher in recurrent meningiomas compared to non-recurrent ones. Convergent to this energetic support, 24 genes related to cell cycle were upregulated in GII, and importantly, the expression of 21 of them was significantly higher in recurrent tumors (SFig. 4, STable4). All these genes discriminated GII from GI meningiomas when upregulated with significant ROC-AUC (STable4). Interestingly, 8 genes related to mitochondrial processes were also significantly upregulated in GII, especially in recurrent meningiomas (SFig.4, STable4).

Cluster 2 with 196 genes showed enrichment in actin filament-based organization and regulation of cell morphogenesis. Twenty-two genes presented significant differential expression levels, and among these, 12 genes presented higher expression, and discriminated M from T and F subtypes (Fig.3A, STable4).

Cluster 3 with 137 genes presented enrichment of biological processes related to leukocyte migration, involved in immune response, and 38 genes presented lower expression in GII compared to GI, with high discriminative power for GII. Interestingly, the expression levels of genes coding for the immunoproteasome were higher in GII compared to GI cases (Fig.4A, B and C), and presented a negative correlation with *EZH2* expression, particularly *HLA-E* and *HLA-F* (Fig.4D). Particularly, *HLA-E* and *WIPF1* expression levels were significantly lower in recurrent compared to non-recurrent meningiomas. In addition, another 12 genes showed significant connectivity to *HLA-E*, *HLA-F*, and *WIPF1* and were negatively correlated to *EZH2* expression (SFig.5, STable4).

Cluster 4 with 472 genes presented enrichment of biological processes related to cell-substrate adhesion with an extracellular matrix (ECM) structural constituent and to negative regulation of cell migration. Among these, 63 genes presented differential expression levels for GI compared to GII, and 44 genes discriminated the F type (Fig.3B, STable4). We identified genes coding for ECM components as collagens (*COL1A2, COL8A1/2*), fibulin (*FBLN1*), elastin (*ELN*), matrilin (*MATN2*), a secreted protein similar to fibrinogen (*FGL2*), and netrin (*NTN1/4*). Moreover, we found genes related to TGFβ that stimulate the synthesis of ECM components (*TGFB3*; *GDF10)*, and related to the

regulation of TGFβ bioavailability (*LTBP1/2*). These genes were differentially upregulated in F-GI and downregulated in GII. Interestingly, *EGFL6*, a regulator of epithelial-mesenchymal interaction, presented the highest score to discriminate F meningioma, corroborating a previous report of its involvement in F meningioma pathogenesis through the PI3K/Akt cell cycle and TGFβ pathways[19]. Notably, *AR* expression levels also discriminated F meningioma, and it correlated negatively with *EZH2* expression among GI meningiomas. A reciprocal regulation between *AR* and *ZEB1* was previously described in breast cancer. ZEB1 is a transcription factor that plays a major role in regulating the epithelial to mesenchimal transition (EMT), and it may be activated by cytokines as TGFβ[20] (Fig. 3B, 5A). Additionally, genes involved in the negative regulation of cell migration (*CYP1B1*, *EMILIN1*, *ENG*, *IGFBP5*, *MMP28*, *PODN*, *PTPRU*) were downregulated in GI in contrast particularly to fibrous-GI, which presented upregulation. (Fig.3B, STable4). Of note, the CYP1B1 expression level impacted the clinical outcome, being among the top 5 genes presenting the highest score to predicted OS and DFS (Fig 5B).

The differentially expressed genes of the four clusters presented high connectivity (Fig.5), and a set of genes related to cell division and negative regulation of cell migration were predictive of overall survival and disease-free survival. Interestingly, *MN1*, meningioma 1, previously described as related to meningioma pathogenesis was one of them (Fig.5).

Immunohistochemistry

A significant difference in EZH2 protein distribution was observed, being cytoplasmic in GI, particularly in M type, and predominantly nuclear in GII with the highest scores in the recurrent meningiomas (Fig.6).

DISCUSSION

Atypical and recurrent meningiomas presented enhancement of oxidative metabolism and cell division

Tumor cells require high energy and substrates to grow and divide, and they need to control the redox potential and reactive oxygen species (ROS) to survive. The levels of

all these metabolites establish the biosignature of what is called metabolic aggressiveness[21]. In fact, the transcriptomic analysis of our meningioma cohort revealed a metabolic reprogramming with upregulation particularly of OXPHOS in GII compared to GI, with a significantly higher expression in recurrent meningiomas. Additionally, an upregulation of genes related to mitochondrial processes was detected in GII. Moreover, the OXOPHOS gene expressions strongly correlated to *PPARGC1A* (also known as *PGC1α*), and *ESRRA* expression levels. ESRRA is an orphan nuclear receptor, which interacts physically with PCG1α at the promoters of OXPHOS-related genes, increasing their expression consistent with our finding of tight co-expression of OXPHOS genes. The higher *PGC1α* expression in GII compared to GI, and particularly in recurrent meningiomas corroborates previous reports of its upregulation in proliferative tumor cells increasing their mitochondrial respiration capacity[22]. The significant upregulation of the major regulator of mitochondrial DNA replication/transcription, *TFAM*, observed in GII is also convergent with the role of *PGC1α* in mitochondrial biogenesis[23]. However, the co-expressions among OXOPHOS genes coded by mitochondrial and nuclear genomes detected in GI were lost in GII, suggesting a decoupling of the electron transport chain that may lead to the production of reactive oxygen species (ROS). ROS mediates the interplay between the regulatory genes and metabolites and modulates several oncogenic signaling pathways[24], which culminates in tumor cell proliferation. In fact, the expression of several genes related to cell division, particularly related to regulation of G2/M transition of mitosis was upregulated in GII, and mostly in recurrent meningiomas. Moreover, a significant upregulation of *EZH2* was observed in recurrent meningiomas, suggesting activation of the *E2F1-EZH2* axis, previously associated with tumor aggressiveness[25]. In fact, EZH2, a cardinal catalytic subunit of polycomb repressive complex 2 (PRC2) has been shown to be downstream in the cell cycle-retinoblastoma-E2F pathway, and is required for the expression of proliferative genes and for E2F-driven proliferation[26]. Interestingly, a recent study pointed out that concomitant overexpression of *EZH2* and *TOP2A* have provided a novel direction for the risk stratification of aggressiveness and a new combinatory therapeutic approach for the clinical management of prostate cancer[27]. Our results also suggest that such a combinatory therapy targeting EZH2 and genes related to cell division may offer an alternative therapeutic strategy for aggressive meningiomas.

Atypical and recurrent meningiomas presented immune evasion associated to *EZH2* upregulation and its nuclear localization

Cancer cells proliferate by evading innate and adaptive systems. Tumor foreign antigens should be presented to the surface of tumor cells bound to major histocompatibility class I (MHC-I) molecules to be recognized by CD8+ cytotoxic T cells for their elimination. Any suppression of the MHC-I system may provide advantages to cancer cells. A very recent study identified an essential role for PCR2 in maintaining transcriptional repression of MHC-I catalyzed by EZH2[28]. We also found that GII meningiomas, particularly the recurrent tumors, presented low expression of MHC-I related genes, which correlated inversely to overexpressed *EZH2*, and its nuclear distribution, particularly *HLA-E* and *HLA-F*. Additionally, we found downregulation of several components of immune processes also negatively correlated to *EZH2*: a) the immunological synapse formation corresponding to molecular movements through remodeling of the actin cytoskeleton (*NCKAP1L*, *DOCK2*); b) cytosolic adaptor proteins involved in immune cell activation (*HCST*, *PSTPIP1, AIF1, P2RX4*); c) inside-out signaling for T-cell activation through integrin stimulation (*VAV1*); d) a regulator of the type I interferon response (*ARRB2*); and e) modulator of leukocyte adhesion and migration (*ITGAM*). Moreover, the downregulation of *WIPF1* has been linked to immune deficiency. Thus, the identified expression profile was consistent with the presence of immune evasion in GII meningiomas.

Genes related to actin cytoskeleton organization and extracellular matrix remodeling were downregulated in atypical and recurrent meningiomas

Several genes related to the reorganization of the actin cytoskeleton, cell adhesion and negative regulation of migration were downregulated in GII, which were convergent with the invasive characteristics presented by the atypical meningiomas. Among them, *CYP1B1*, identified as a gene involved in cell motility, presented negative and significant scores in determining clinical outcomes, indicating that the downregulation of their expression impacted shorter overall survival and disease-free survival time. Interestingly, the meningioma 1 (*MN1*) gene was also identified as one of the top 5 genes predicting a clinical outcome. It is located in Chr 22q12.1 close to the *NF2* gene (Chr 22q12.2), and

it functions as a transcriptional coactivator. It has been suggested that the inactivation of this gene contributes to meningioma pathogenesis[29].

In summary, the transcriptomic analysis of our meningioma cohort identified a set of differentially expressed genes in grade II related to the activation of oxidative metabolism, cell division, cell motility due to extracellular remodeling, and immune evasion. Among them, the genes related to cell cycle and ECM remodeling were predictive of clinical outcomes, and may be potential candidates to monitor meningioma evolution. They may also be targets for adjuvant therapeutic strategies.

Acknowledgements

We are grateful to the São Paulo Research Foundation (FAPESP 2001/12898-4, 2004/12133-6, 2013/02162-8, 2014/50137-5); to the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 305730/2015-0) and to FMUSP and the Fundação Faculdade de Medicina (FFM).

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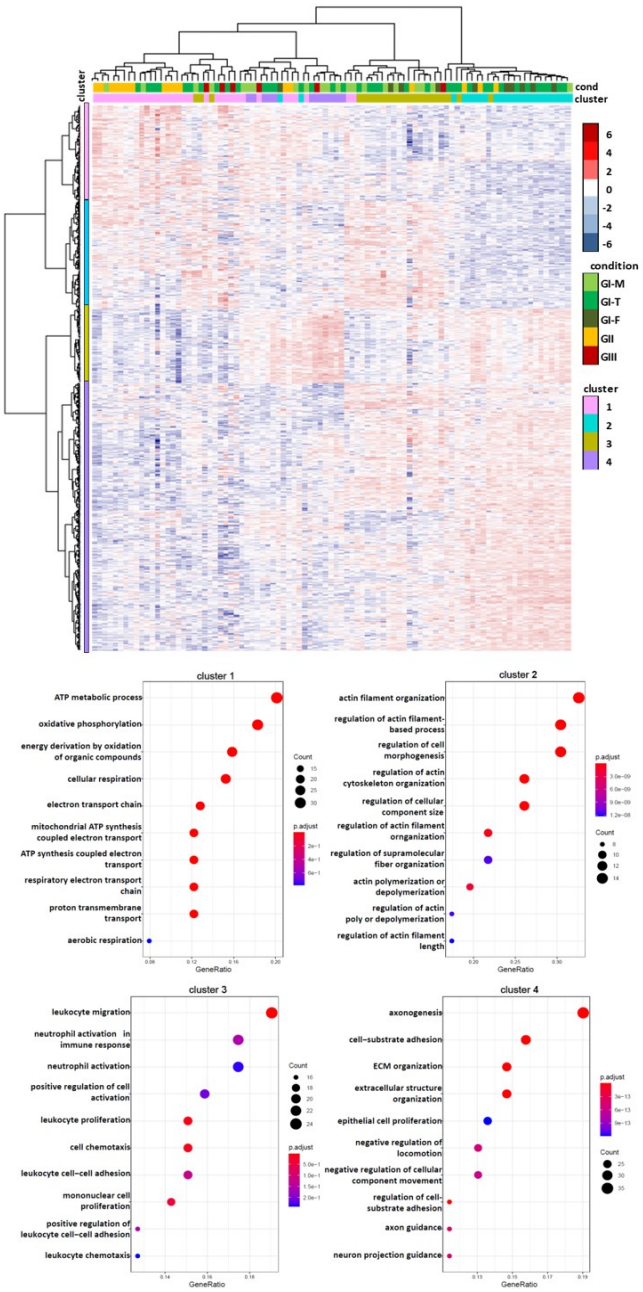


Figure 1. Transcriptomic analysis of 91 meningiomas. **A**. Unsupervised clusterization identified 4 cluster showing in red the upregulated genes and in blue the downregulated. **B**. Dot plots illustrating the top 10 most enriched Gene Ontology terms of Biological Process for the gene set of each cluster

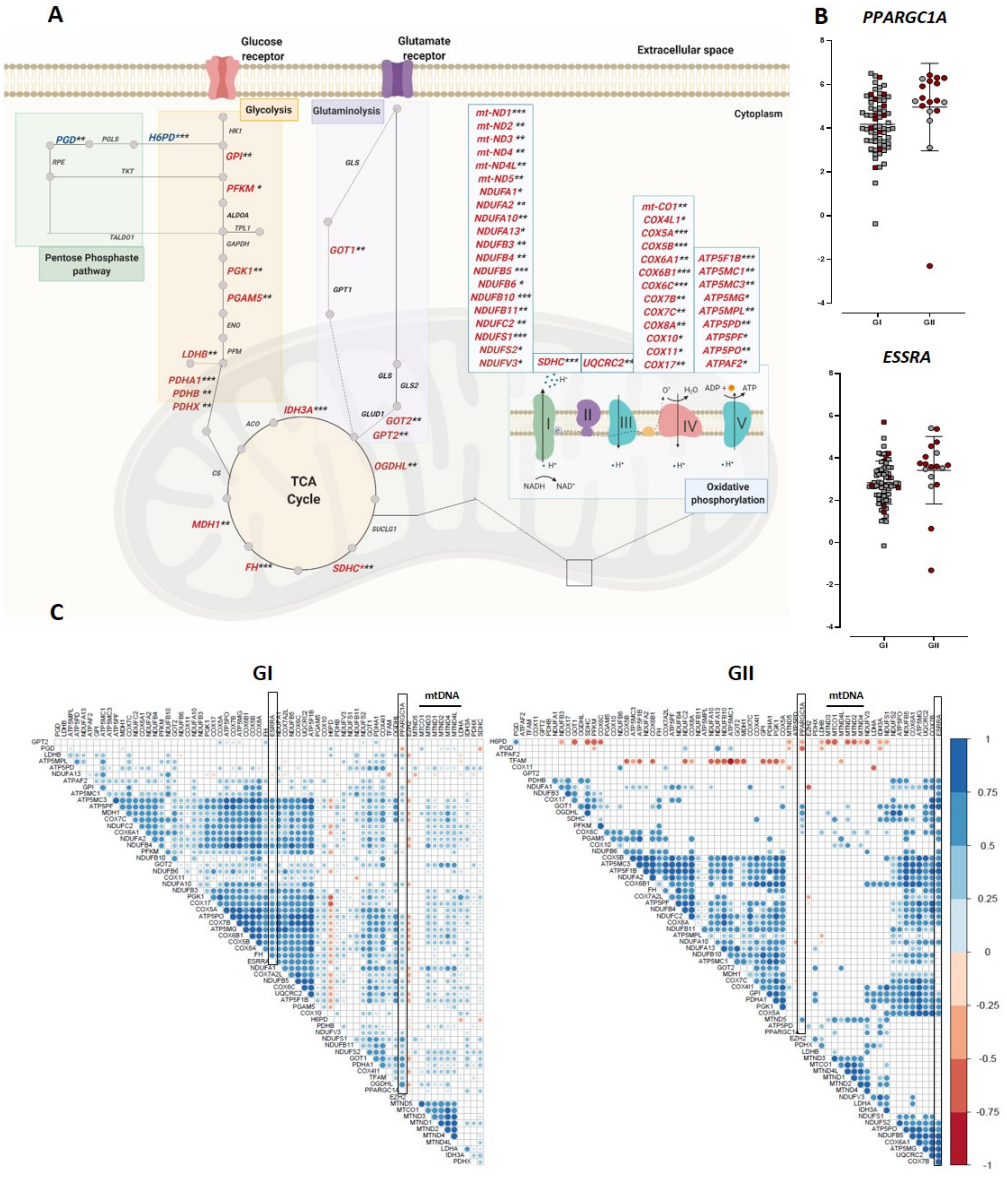


Figure 2. **Cluster 1: genes enriched for metabolic process, particularly the oxidative phosphorylation**. **A**. The upregulated genes in meningiomas grade II (GII) compared to grade I (GI) in glycolysis, TCA cycle, oxidative phosphorylation (OXPHOS) and glutaminolysis are plotted in red. The pentose phosphate pathway related genes *H6DP* and *PGD* were downregulated and they are shown in blue. * p≤0.05, ** p≤0.005 and *** p≤0.0005 by Kruskal-Wallis test. **B**. *PPARGC1A* and *ESRRA* expressions were upregulated in GII compared to GI (p=0.002 and p=0.008, respectively, Kruskal-Wallis test). In red are demonstrated the recurrent meningiomas, and *PPARGC1A* expression was significantly higher in recurrent compared to non-recurrent cases (p=0.032, Mann-Whitney test). **C**. Correlation matrix showing the gene expression correlations with each other in GI and GII. Positive correlations are shown in blue and negative correlations in orange. The color intensiveness and the size of the circle are proportional to the value of r by Spearman test (scale presented at right side). Only the correlations with $p < 0.05$ were plotted. The correlations among the OXPHOS related genes and *ESRRA* were reinforced in GII. *TFAM*, a transcription regulator of mitochondrial-OXPHOS genes, correlated negatively to genes coded by nuclear genome (*ATP5MC1*, r=-0.88, p=0.000; *NDUFB10*, r=-0.72, p=0.001; *NDUFA13*, r=-0.67, p=0.002). The correlations with mitochondrial genome coded OXPHOS genes (mtDNA) observed in GI was partially lost in GII.

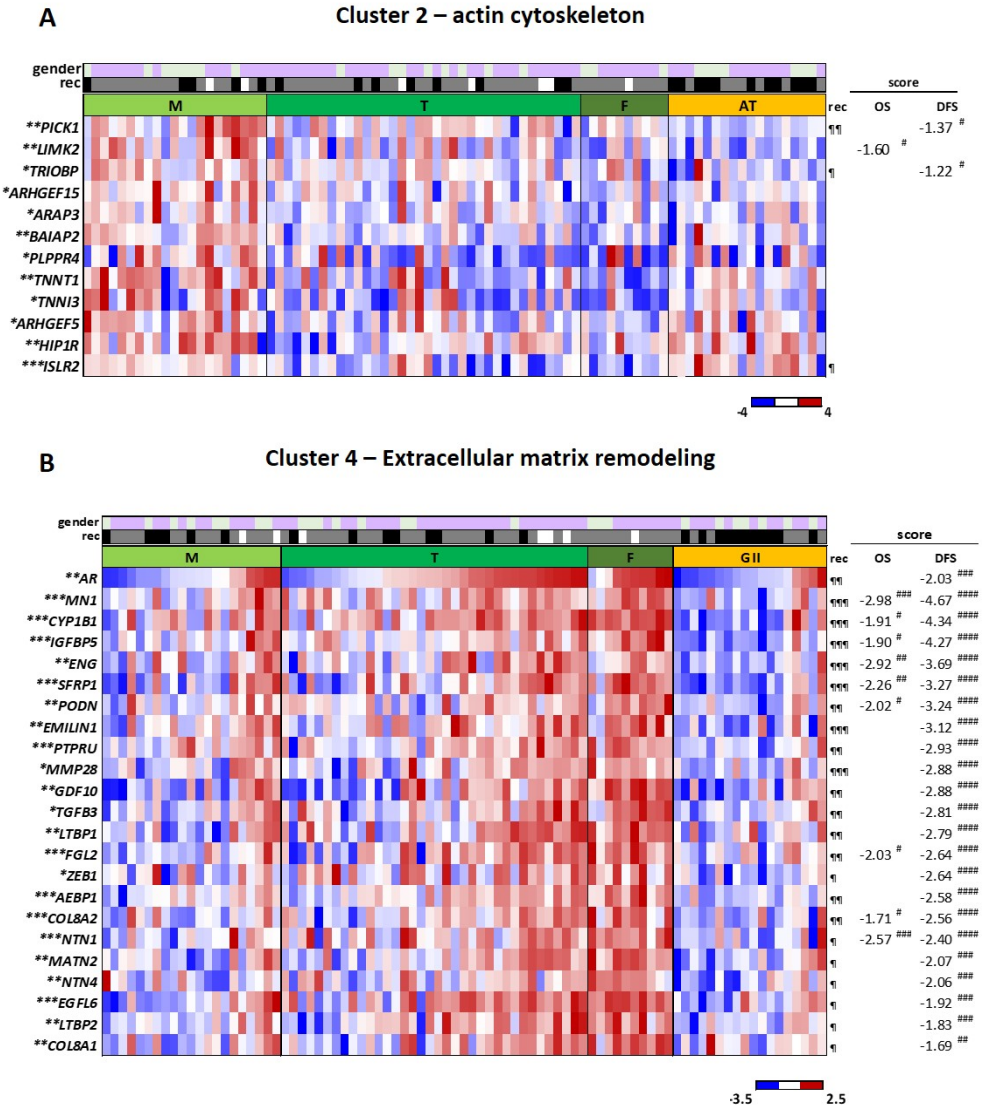


Figure 3. A. Cluster 2: genes enriched for actin cytoskeleton. Heatmap of expression levels of 12 genes highly connected with actin filament organization with differential expression levels among GI histological subtypes, presenting higher expression in meningothelial (M) compared to transitional (T) and fibrous (F) meningiomas (*p≤0.05, **p≤0.005, ***p≤0.0005, Kruskal-Wallis test; all genes presenting p≤0.05, Dunn test; ROC-AUC≥0.665 with p≤0.032). *LIMK2*, *BAIAP2*, *ARGHGEP5/15, ARAP3, and RHOJ* are associated to downstream effector of Rho small G proteins, coding for proteins involved with lamellipodia, filipodia, stress fibers, focal adhesion formation and cell shape regulation. *ISLR2* expression level was significantly lower among recurrent meningiomas (¶: p=0.018, Mann-Whitney test). **B. Cluster 4: genes enriched for extracellular matrix**. Heatmap of 23 genes presenting higher expression in F compared to M and T, and also discriminated F type (*p≤0.05, **p≤0.005, ***p≤0.0005, Kruskal-Wallis test; all genes presenting p≤0.05, Dunn test; ROC-AUC≥0.694, p≤0.046). *EGFL6* presented high score to discriminate F meningioma (ROC-AUC 0.843, p=0.0001). *AR* expression level showed significant power to discriminate F type (ROC-AUC=0.759, p=0.008), with higher expression than M and GII meningiomas (p=0.004, and p<0.0001 respectively, Dunn test). Significant lower expression levels of these genes were observed in recurrent meningiomas (¶p≤0.05, ¶¶p≤0.005, ¶¶¶p≤0.0005, Mann-Whitney test). Each line represents the z-score of logCPM values. CPM: counts per million. Female: pink, male in light-green. Recurrent meningioma: black, non-recurrent: grey, lost follow-up: white. M: meningothelial, T: transitional, F: fibrous, GII: grade II atypical meningioma, OS: overall survival, DFS: disease free survival. Score: T-statistic value comparing the gene expression level among the alive and dead patients for OS, and non-reccurent and reccurent cases for DFS. #: q-value as the lowest False Discovery Rate at which each gene was called significant based on the work of John Storey(142). (#<20%, ##<10%, ###<5%, ####<1%).

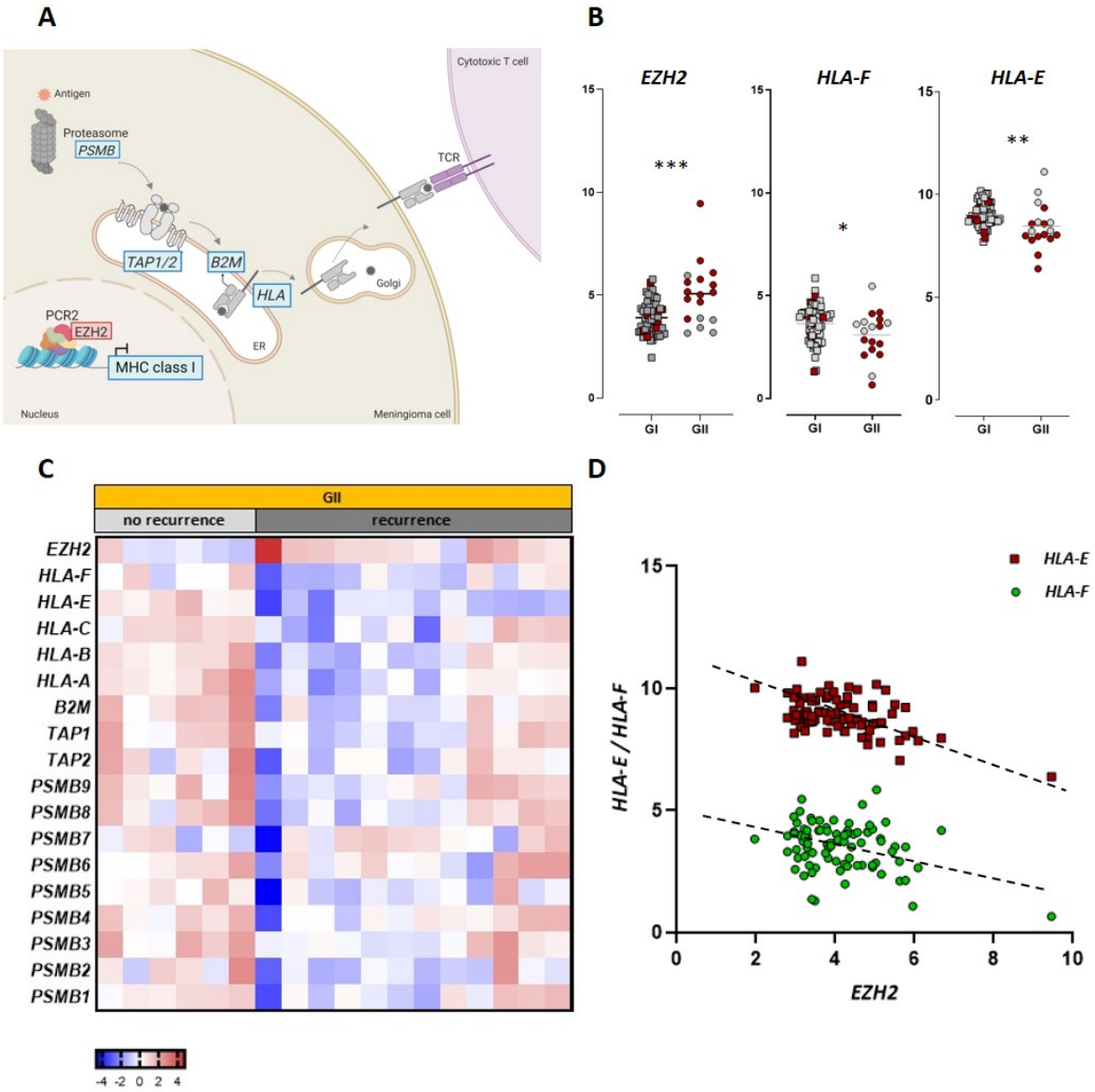


Figure 4. **Cluster 3: genes enriched for immune response. A.** The MHC-I antigen processing involves multiple steps including immuno proteasome components (PSMBs), peptide transporters associated with antigen processing (TAP1, TAP2), scaffold stabilizer (B2M), and MHC-I-heavy chain (HLAs) molecules, which display intracellular peptides on the cell surface for $CD8^+$ T cell recognition. EZH2 represses the transcription of MHC-class I related genes(143). **B.** *EZH2* expression was higher in GII meningiomas compared to GI (p=0.001, Mann-Whitney test), particularly recurrent (in red) compared to non-recurrent cases (p=0.003, Mann-Whitney test). In contrast *HLA-F* and *HLA-E* expressions were downregulated in GII (p=0.031 and 0.001, respectively, Mann-Whitney test). *HLA-E* expression was significantly lower in recurrent meningiomas (in red) (p=0.014, Mann-Whitney test). **C.** Heatmap representing RNASeq expression of the genes coding for proteins involved in the MHC-class I pathway in GII recurrent and non-recurrent meningiomas. A negative correlation of these genes with EZH2 expression was observed among recurrent GII meningiomas. Each line represents the z-score of logCPM values. CPM: counts per million. **D.** Negative correlation among the expressions of *EZH2/HLA-E (p=0.0006, r=-0.3475)* and *EZH2/HLA-F (p=0.0337, r=-0.1993*). The *EZH2/HLA-E* negative correlation was more significant among recurrent meningiomas (p=0.0004, r=-0.6589, Spearman rho test).

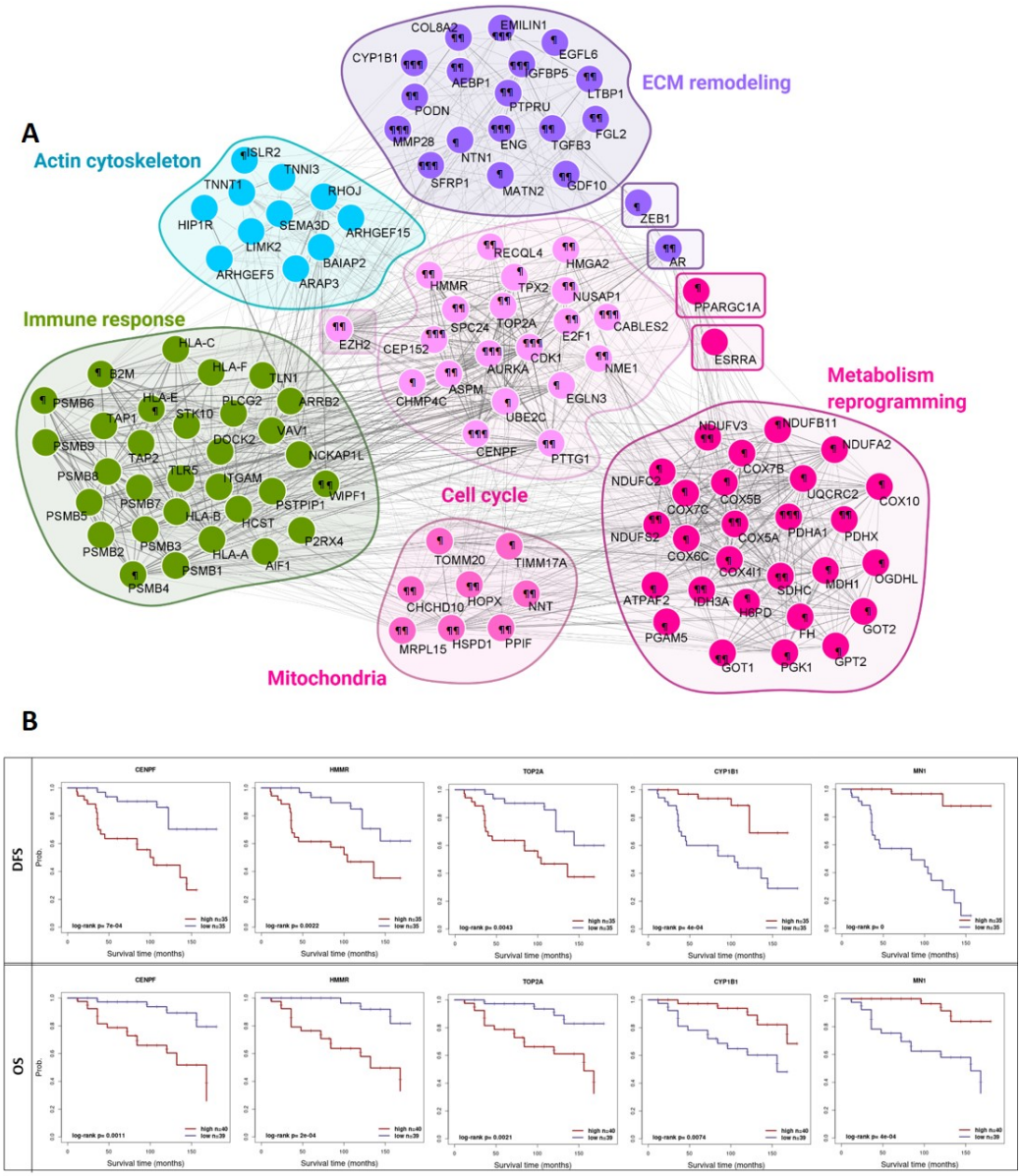


Figure 5. **Connectivity and clinical impact of the identified genes in the analyzed clusters**. **A**. The network of proteins related to pathways identified in WebGestalt analysis performed by String app in Cytoscape software. The proteins are represented by nodes and the interactions are represented by edges (score value≥0.5). Cluster 1: metabolism reprogramming, cell cycle, and mitochondria (nuances of pink); Cluster 2: actin cytoskeleton (blue); Cluster 3: immune response (green); and Cluster 4: extracellular matrix (ECM) remodeling (lilac). Significant differential gene expressions between recurrent and non-recurrent meningiomas are represented: ¶ p<0.05; ¶¶ p<0.005; ¶¶¶ p<0.0005 (Mann-Whitney test). **B**. Kaplan-Meier curves for overall survival (OS) and disease free survival (DFS) of the top 5 genes presenting significant score and q-value calculated by Samr. Meningioma patients presenting hyperexpression of *CENPF*, *HMMR* and *TOP2A,* genes related to cell cycle identified in cluster 1, presented shorter OS and DFS compared to those presenting hypoexpression. In contrast to the expression level *CYP1B1*, related to extracelular matrix remodeling of cluster 4, which hiperexpression correlated to better outcome. Similarly, *MN1* hyperexpression confered better clinical outcome. High (red) or low (blue) expression was determined relative to the median expression value for each gene in 70 cases. Meningioma patients who died in the immediate post-surgical period, due to causes not-related to the tumor progression and with discontinued follow-up were excluded for this analysis.

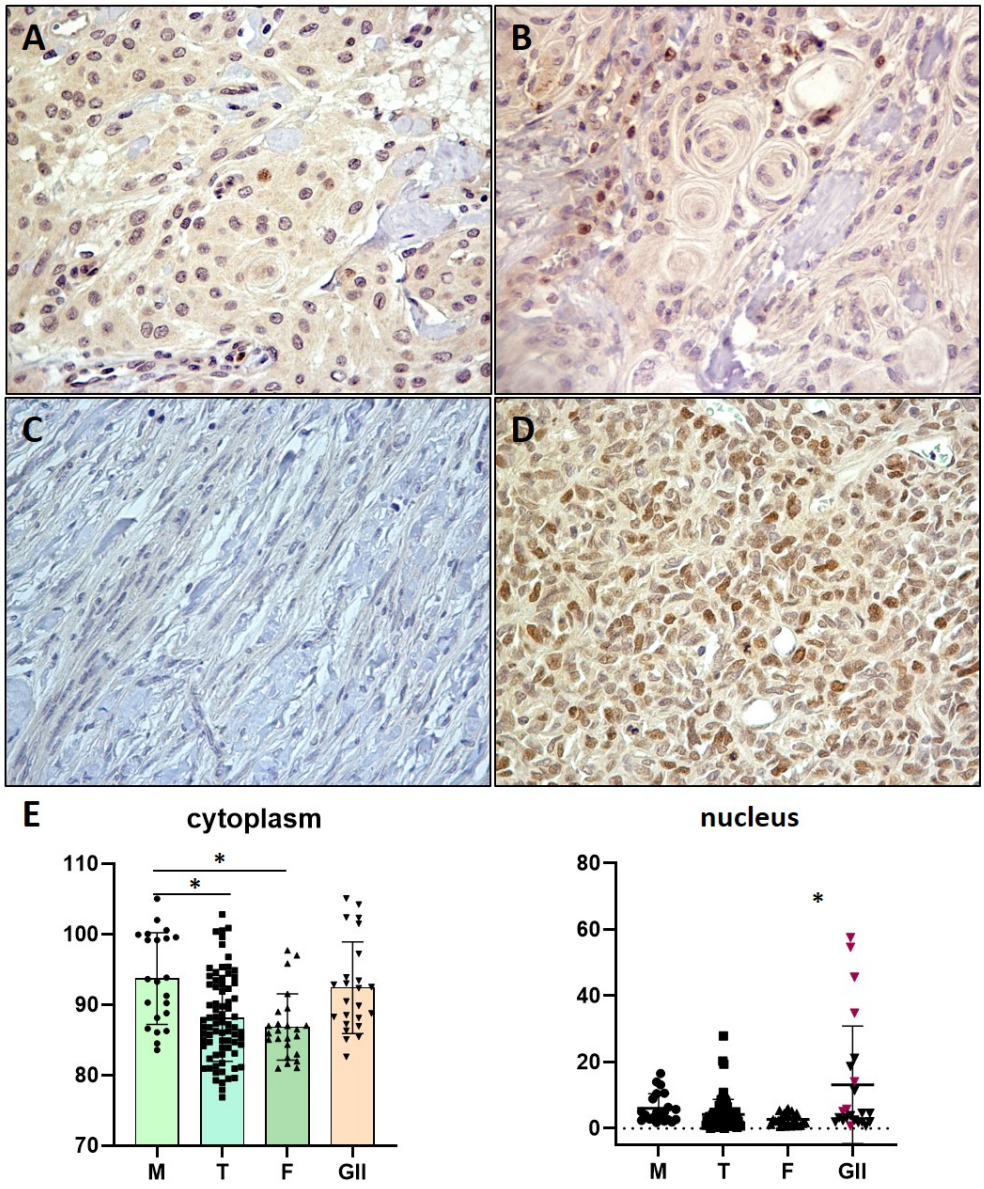
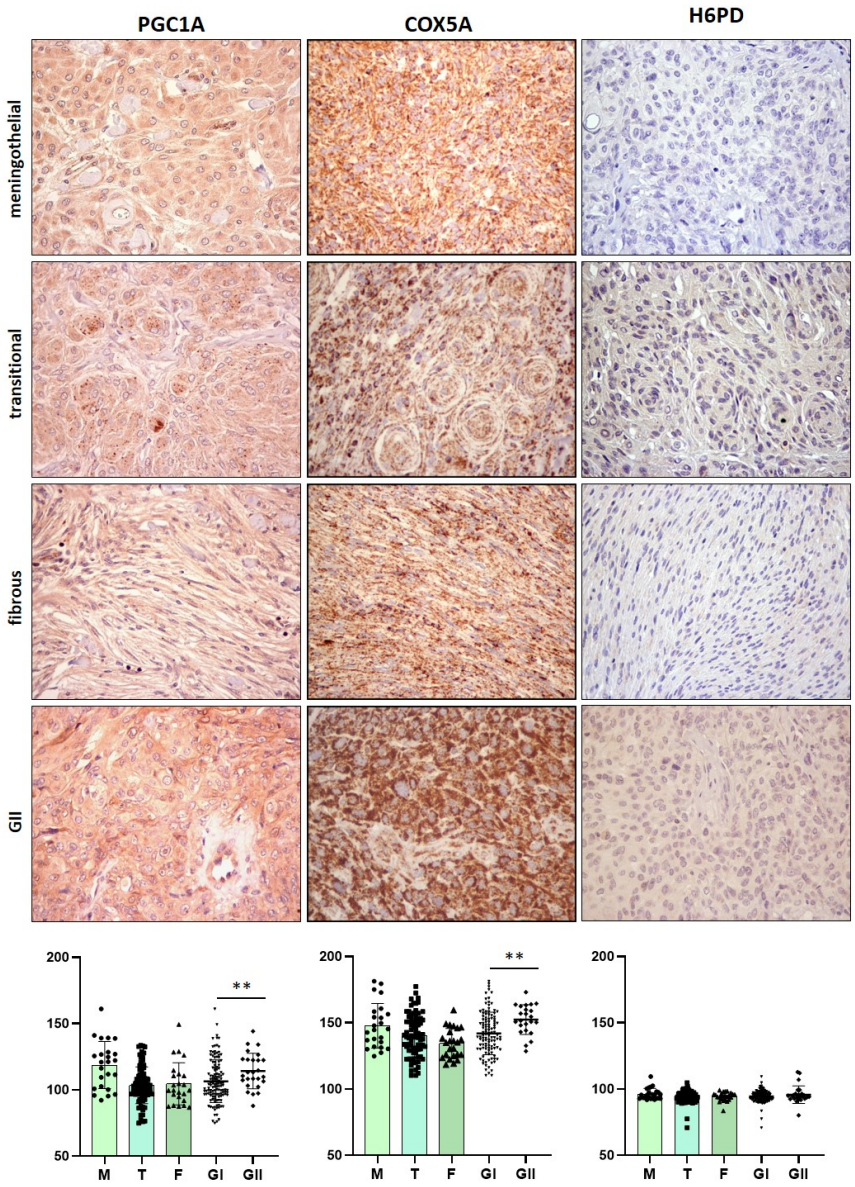
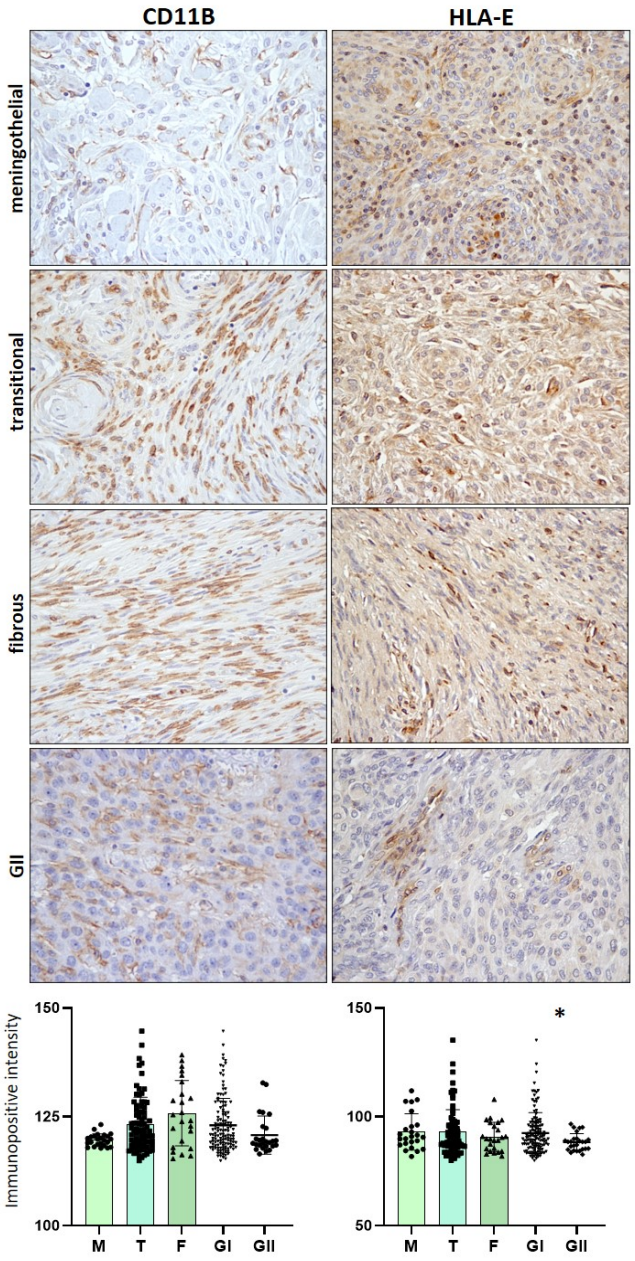


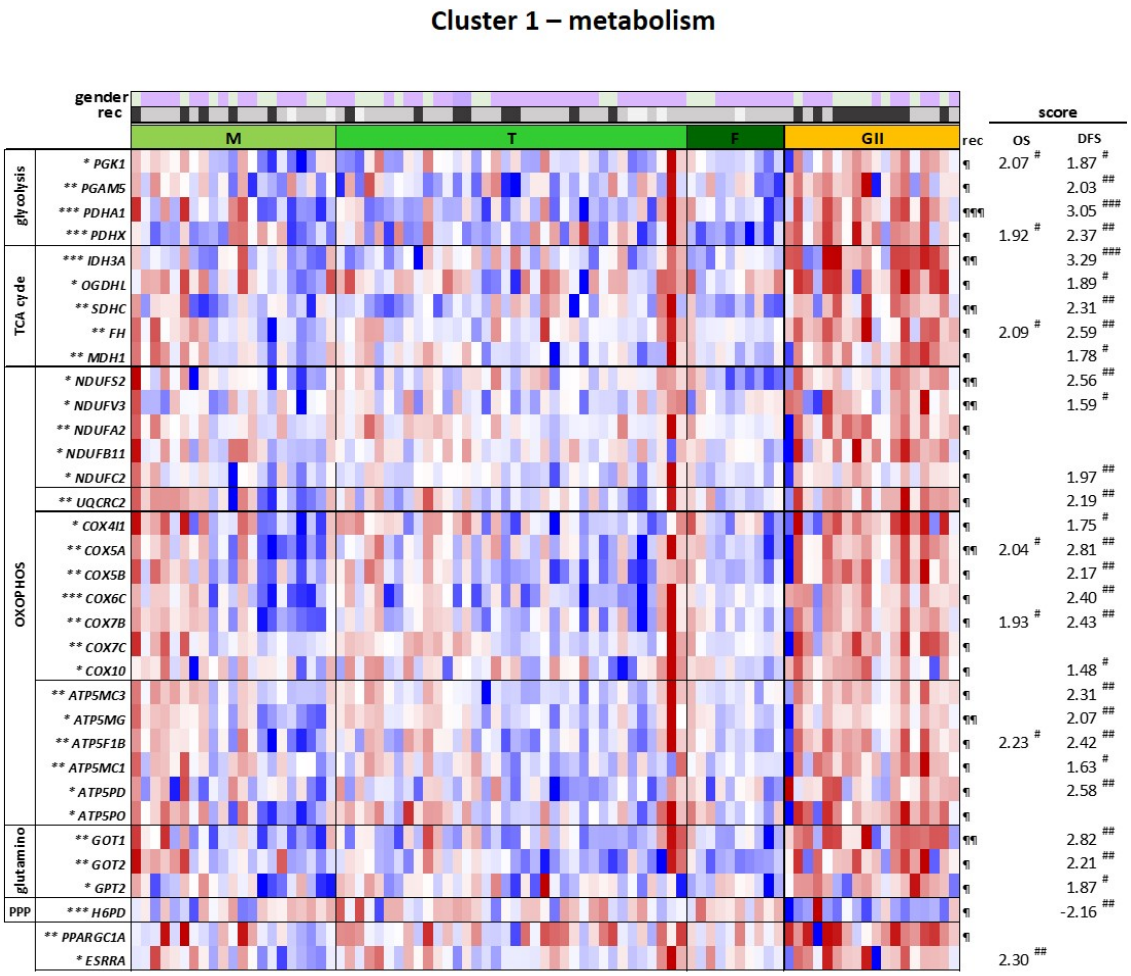
Figure 6. Cytosolic and nuclear EZH2 protein expression in GI meningothelial-M (**A**), transitional-T (**B**), fibrous-F (**C**) and GII (**D**) meningiomas. **E.** Intensity of EZH2 immunoreactivity in the cytoplasm measured by Image J color deconvolution, and the percentage of positive nuclei for EZH2 relative to total number of nuclei. EZH2 cytoplasmic immunoreactivity was significantly different among the analyzed groups (p=0.001, Kruskal-Wallis test), and it was higher in M compared to T (p=0.0009) and F (p=0.002), as it was higher in GII compared to T (p=0.005) and F (p=0.008). EZH2 nuclear positivity was significantly higher in GII, particularly among the recurrent meningiomas (red) (GII x T p=0.0365, GII x F p=0.0109). The recombinant Anti-KMT6 / EZH2 antibody (ab191080) was used in 1:2000, pH=9.3. Representative microscopical images are presented in 400x magnification.



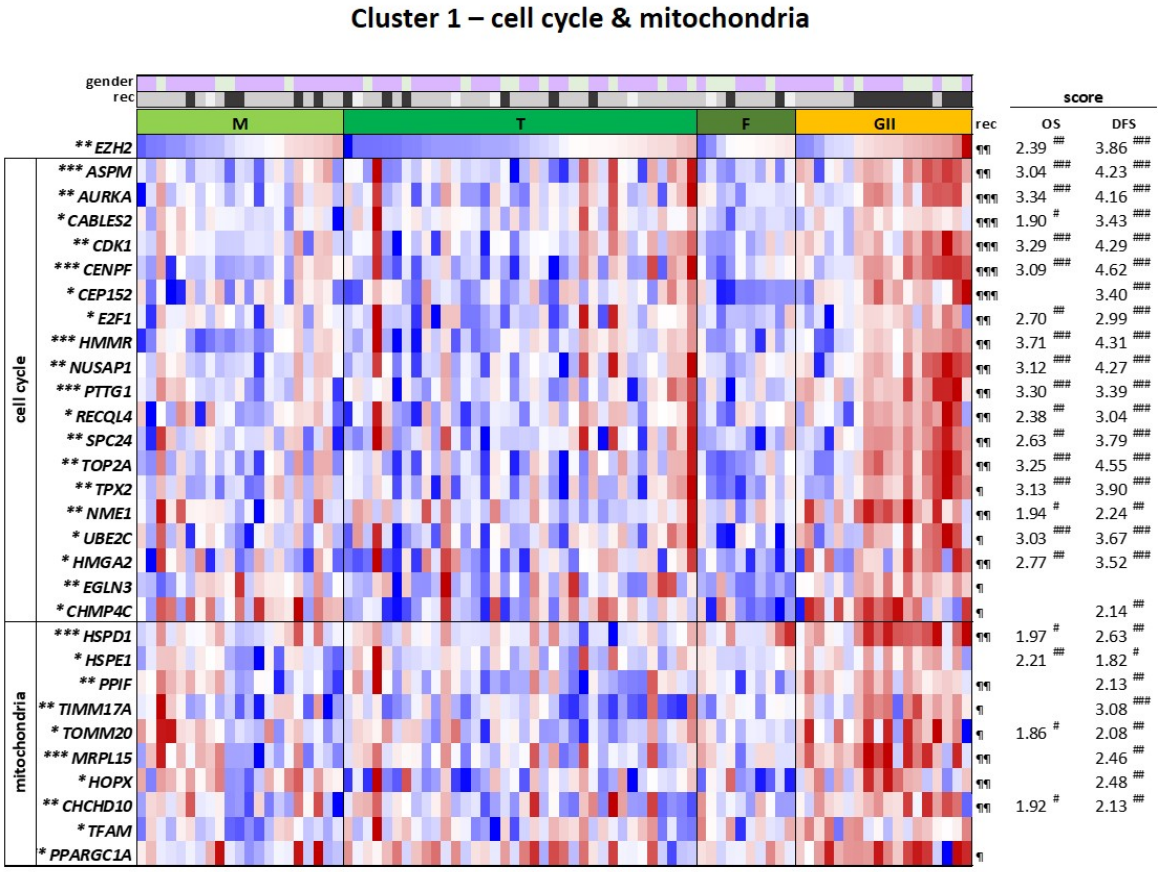
Supplemental Figure 1. **Immunohistochemistry for PGC1A, COX5A, and H6PD** for GI meningothelial (M), transitional (T) and fibrous (F) histological types, and GII atypic meningioma. Higher PGC1A and COX5A protein expressions were observed in GII compared to GI (p=0.0084 and p=0.0015, respectively, Mann-Whitney test). In contrast, low H6PD protein expressions were observed in GI and GII (p=0.6944, Mann-Whitney test). Anti-PGC1A rabbit polyclonal, ab54481, 1:400, pH=6.3); anti-COX5A rabbit monoclonal ab110262, 1:1600, pH=6.3 and anti-H6PD rabbit monoclonal, ab170895, 1:50, pH=9.3 were used for immunohistochemistry. Representaive images were presented in 400x magnification. The values of immunopositive intensity obtained by Image J color deconvolution were used for statistical analysis.



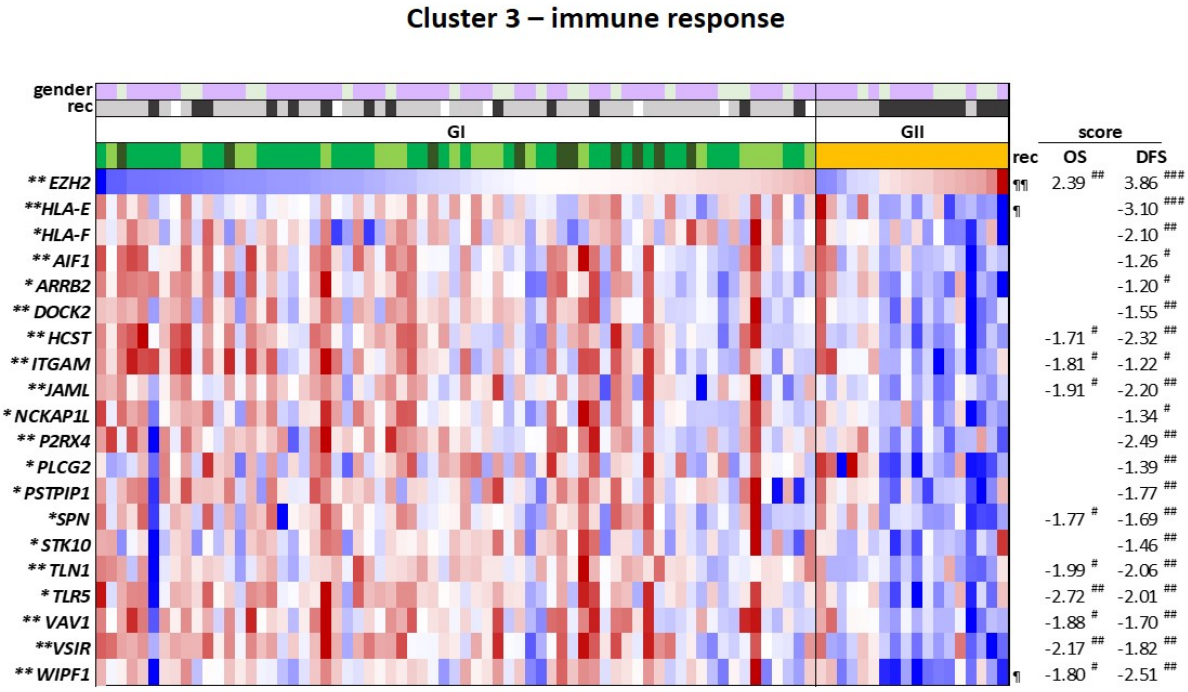
Supplemental Figure 2. **Immunohistochemistry for CD11B (ITGAM), and HLA-E** for GI meningothelial (M), transitional (T) and fibrous (F) histological types, and GII atypic meningioma. Lower CD11B and HLA-E protein expressions were observed in GII compared to GI ($p<0.0001$ Kruskal-Wallis test and M x T $p<0.001$, M x F $p<0.0001$, M x GII $p=0.015$, T x GII $p=0.023$, F X GII $p=0.008$ Dunn test for CD11B; $p=0.020$ Kruskal-Wallis test and M x GII $p=0.008$, T x GII $p=0.038$, F x GII $p=0.004$, GI x GII $p=0.038$ Dunn test for HLA-E). Anti-CD11B rabbit monoclonal, ab52478, 1:2000, pH=6.3); anti-HLA-E mouse monoclonal ab2216, 1:1600, pH=6.3 were used for immunohistochemistry. Representaive images were presented in 400x magnification. The values of immunopositive intensity obtained by Image J color deconvolution were used for statistical analysis.



Supplemental Figure 3. A. Cluster 1: genes enriched for metabolic reprogramming. Heatmap of expression levels of 34 genes highly connected being 4 genes related to glycolysis, 5 to TCA cycle, 19 to oxidative phosphorylation (OXPHOS), 3 to glutaminolysis, 1 to pentose phosphate pathway (PPP), and PPARGC1A and ESRRA. Upregulated gene expression was observed in GII, except for *H6PD* (*p≤0.05, **p≤0.005, ***p≤0.0005, Kruskal-Wallis test; p≤0.05, Dunn test; ROC-AUC≥0.60, p≤0.032). Their expression levels were also higher in recurrent compared to non-recurrent meningiomas, except for *ESRRA* ((¶p≤0.05, ¶¶p≤0.005, ¶¶¶p≤0.0005, Mann-Whitney test). OS: overall survival, DFS: disease free survival. Score: T-statistic value comparing the gene expression level among the alive and dead patients for OS, and non-reccurent and reccurent cases for DFS. #: q-value as the lowest False Discovery Rate at which each gene was called significant based on the work of John Storey(142). (#<20%, ##<10%, ###<5%, ####<1%).



Supplemental Figure 4. A. Cluster 1 genes enriched for cell cycle and mitochondrial function. Heatmap of expression levels of 19 genes highly connected and related to regulation of mitotic cell cycle (*AURKA, CENPF, CEP152, CDK1, E2F1, RECQL4, TOP2A, HMMR, PTTG1, NUSAP1, TPX2, UBEC2C, HMGA2, CHMPAC)*, to cell division (*ASPM, CABLES2, SPC24*), to genomic stability (*NME1*) and to cellular response to hypoxia (*EGLN3*). The expression of these genes was correlated to *EZH2* expression particularly in GII. Ten genes were also highly connected and related to mitochondrial processes as to protein import into mitochondria (*HSPD1*); to protein targeting to mitochondria (*TIMM17A*, *TOMM20*; *CHCHD10*), to transmembrane transport (*NNT*); to protein synthesis within the mitochondria (*MRPL15*); to chaperone-mediated protein complex assembly (*HOPX*); to protein folding and mitochondrial permeability transition pore in the inner mitochondrial membrane (*PPIF*); and to mitochondrial genome transcriptional machinery (*TFAM*, *PPARGC1A*). The expressions of these genes were higher in GII compared to GI (*p≤0.05, **p≤0.005, ***p≤0.0005, Kruskal-Wallis test; p≤0.05, Dunn test; ROC-AUC≥0.060, p≤0.032). Their expression levels were also higher in recurrent compared to non-recurrent meningiomas, except for *HSPE1 and TFAM.* (¶p≤0.05, ¶¶p≤0.005, ¶¶¶p≤0.0005, Mann-Whitney test). OS: overall survival, DFS: disease free survival. Score: T-statistic value comparing the gene expression level among the alive and dead patients for OS, and non-reccurent and reccurent cases for DFS. #: q-value as the lowest False Discovery Rate at which each gene was called significant based on the work of John Storey(142). (#<20%, ##<10%, ###<5%, ####<1%).



Supplemental Figure 5. A. Cluster 3 genes enriched for immune response. Heatmap of expression levels of additional 14 genes highly connected and related to immune response, which presented significant lower expression in GII compared to GI. (*p≤0.05, **p≤0.005, ***p≤0.0005, Kruskal-Wallis test; p≤0.05, Dunn test; ROC-AUC≥0.6440 with p≤0.036). A significant negative correlation of *EZH2* expression was observed in GII meningiomas with *VAV1* (r=-0.717, p=0.001), *ARRB2* (r=-0.651, p=0.003), *NCKAP1L* (r=-0.649, p=0.004), *ITGAM* (r=-0.585, p=0.011), *HCST* (r=-0.571, p=0.013), *AIF1* (r=-0.501, p=0.034), *PSTPIP1* (r=-0.492, p=0.038), *P2RX4* (r=-0.486, p=0.041) and *DOCK2* (r=-0.478, p=0.045). *WIPF1* expression was significantly lower (¶ p=0.019), in contrast to higher expression of EZH2 (¶¶ p=0.003) in recurrent compared to non-recurrent meningiomas. OS: overall survival, DFS: disease free survival. Score: T-statistic value comparing the gene expression level among the alive and dead patients for OS, and non-reccurent and reccurent cases for DFS. #: q-value as the lowest False Discovery Rate at which each gene was called significant based on the work of John Storey(142). (#<20%, ##<10%, ###<5%, ####<1%).

Table 1: clinical data

Clinical data		
Gender	Female	62
	Male	29
Follw-up	Mean age (years old)	54.87 ± 13.85
	Follow-up (months)	90.81 ± 51.32
Hitological subtype	GI - Transitional	36
	GI - Meningothelial	21
	GI - Fibrous	10
	GII - Atypical	18
	GIII -Malignant	6
Lozalization	Convextity	63
	Skull Base	26
	Ventricle	2
Death	Death Post-op	4
	Death after PO	16
Recurrence	yes	24
	no	67
	mean time (months)	41.62
	RT after 1st surgery	8

Table 2: Demografic data, tumor localization, clinical follow-up, clinical outcome and somatic mutations

									MLPA	NGS by customized panel								
#case	histology	rec	gender	Age	Localization	reccurence (mo)	follow up (mo)	Death	Loss Chr.22	NF2	AKT1	KLF4	SUMO	SUFU	TERT	TRAF7	SMARCB1	PIK3CA	POLR2A
121	M	1	F	59	Convexity	108	144												
144	M	0	F	55	SB		180												
150	M	ss	F	54	Convexity														
221	M	1	M	31	SB	46	168												
288	M	0	F	36	Convexity		156												
293	M	0	F	70	Convexity		36		y	exon1:c.43_44del:p.K15fs									
303	M	ss	F	45	SB														
304	M	0	M	69	SB		156												
376	M	1	M	37	Convexity	84	156		y	exon1:c.71dupT:p.V24fs									
494	M	1	M	28	Convexity	136	156												
549	M	0	M	73	Convexity		12												
641	M	0	M	76	Convexity		24												
869	M	0	F	22	Convexity		36												
870	M	0	M	50	Convexity		96				exon4:c.G49A:p.E17K					exon19:c.C1837G:p.Q613E			
979	M	0	F	60	Convexity		108												
1102	M	0	F	78	Convexity		72												
1153	M	0	F	51	SB		120												
1215	M	0	F	44	Convexity		120												
1259	M	0	F	49	SB		108									exon13:c.C1172A:p.T391N			
1291	M	0	F	66	SB		72									exon21:c.2006_2019del:p.T669fs			
1392	M	1	M	58	Convexity	84	84		y										
84	T	0	F	54	SB		60		y	exon2:c.G148A:p.V50M									
114	T	1	F	46	Convexity	37	120	y	y										
136	T	1	F	69	Convexity	144	144		homo	exon5:c.G463A:p.A155T,exon6:c.G525A:p.W175X									
212	T	ss	F	47	SB														
219	T	ss	F	68	SB														
223	T	0	F	58	SB		168					c.A1225C:p.K409Q							
231	T	0	M	75	Convexity		24												
308	T	0	F	58	Convexity		168		y	exon10:c.G931T:p.E311X									
333	T	0	F	39	Convexity		24		y										
343	T	0	F	46	Convexity		60		y	exon6:c.491_492insGAACAGAC:p.E164fs									
365	T	0	M	54	Convexity		120												
389	T	1	F	53	Convexity	100	168		y	exon2:c.C169T:p.R57X									
416	T	ss	F	75	SB														
444	T	0	M	35	Convexity		156		y				exon3:c.G583A:p.V195M						
447	T	0	F	41	SB		84												
454	T	0	M	62	SB		iPO	y				c.A1225C:p.K409Q				exon19:c.A1843G:p.K615E			
470	T	1	F	47	Convexity	122	144		y										
484	T	0	M	43	Convexity		144												
551	T	0	F	52	Convexity		168					c.A1225C:p.K409Q				exon17:c.A1559G:p.N520S			
602	T	1	F	48	Convexity	36	120												
626	T	ss	M	66	Convexity														
708	T	0	M	47	Convexity		144		y										
821	T	0	F	77	ventricle		120	y											
830	T	1	F	72	Convexity	36	36	y	y	exon8:c.T698G:p.L233W, exon13:c.1446+1G>T									
844	T	0	F	69	SB		48		y	exon7:c.675+2T>									
970	T	1	F	69	Convexity	122	132												
1004	T	0	F	57	SB		120		y	exon2:c.G148A:p.V50M									
1053	T	0	M	53	Convexity		84	y											
1068	T	0	F	58	Convexity		132												
1089	T	0	F	64	Convexity		120						NM_005631:exon9:c.G1570C:p.A524P						
1110	T	0	F	42	Convexity		72		y										
1266	T	0	F	55	Convexity		108		y				exon12:c.T2342C:p.M781T						
1271	T	0	F	60	Convexity		108		y										
1320	T	0	F	42	SB		108		y										
1321	T	1	F	34	SB	60	108						NM_005631:exon9:c.G1604T:p.W535L						
1388	T	0	F	72	Convexity		84		y	exon6:c.448_465del:p.150_155del									
54	F	0	M	57	Convexity		60		homo										
82	F	0	F	50	Convexity		120		y										
240	F	0	F	45	Convexity		156		y	exon11:c.1122+1G>T									
361	F	0	F	44	SB		168				exon4:c.G49A:p.E17K								
422	F	ss	F	79	SB				y										
434	F	0	F	52	Convexity		96	y			exon4:c.G49A:p.E17K								
475	F	0	F	76	Convexity		iPO	y	y	exon9:c.C781T:p.Q261X									
1186	F	0	F	77	SB		120		y										
1376	F	0	M	51	Convexity		84		y										
1385	F	0	M	44	Convexity		84		homo										
25	GII	0	F	58	Convexity		72		y	exon7:c.675+1G>C									
292	GII	1	M	53	Convexity	35	84		y	exon4:c.C337T:p.R113X									
325	GII	1	M	69	Convexity	12	24		y	exon3:c.C244T:p.Q82X									
430	GII	1	M	39	Convexity	36	36	y	y										
474	GII	0	F	60	Convexity		132		y	exon2:c.222dupT:p.H74fs									
482	GII	1	F	55	Convexity	45	72	y	y	exon2:c.147_163del:p.Y49fs									
489	GII	1	F	64	Convexity	20	24	y	y	exon2:c.207delG:p.Q69fs									
525	GII	0	F	27	SB		108		y	exon3:c.241-1G>T									
777	GII	1	F	65	SB	104	120		y										
924	GII	0	F	80	Convexity		24		y	exon9:c.868_869del:p.A290fs									
954	GII	0	F	33	Convexity		48	y	y	exon2:c.171_172insTT:p.K57fs				exon1:c.C180G:p.Y60X	start:1295250				
960	GII	0	M	60	Convexity		iPO	y	y										
966	GII	1	M	53	Convexity	34	168		y	exon4:c.C337T:p.R113X									
1114	GII	1	M	39	Convexity	36	36	y	y										
1167	GII	1	M	45	SB	24	24		y	exon1:c.C78G:p.I26M									
1213	GII	0	F	74	Convexity		iPO	y	y	exon6:c.441_442del:p.T147fs									
1222	GII	1	F	55	Convexity	40	82		y	exon2:c.147_163del:p.Y49fs									
1314	GII	1	F	58	Convexity	11	96		y	exon10:c.G973T:p.E325X									
102	GIII	0	M	48	Convexity		24	y	y	exon3:c.T254A:p.L85X									
171	GIII	0	F	74	Convexity		72	y	y										
656	GIII	0	F	72	Convexity		36	y											
672	GIII	0	M	35	ventricle		36	y											
1410	GIII	0	M	41	SB		12	y							start:1295228				
348	GIII	0	F	44	SB		132	y											

Table 3: Dotplot analysis

Cluster 1							
ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	Count
GO:0046034	ATP metabolic process	32/70	304/18670	5,71211E-39	5,71211E-39	3,94436E-36	32
GO:0006119	oxidative phosphorylation	30/70	145/18670	9,00153E-46	9,00153E-46	1,24316E-42	30
GO:0015980	energy derivation by oxidation of organic compounds	22/70	286/18670	2,34254E-23	2,34254E-23	3,59463E-21	22
GO:0045333	cellular respiration	22/70	194/18670	3,83113E-27	3,83113E-27	8,81831E-25	22
GO:0022900	electron transport chain	21/70	186/18670	7,35432E-26	7,35432E-26	1,45096E-23	21
GO:0042775	mitochondrial ATP synthesis coupled electron transport	20/70	97/18670	3,3599E-30	3,3599E-30	1,45376E-27	20
GO:0042773	ATP synthesis coupled electron transport	20/70	98/18670	4,21059E-30	4,21059E-30	1,45376E-27	20
GO:0022904	respiratory electron transport chain	20/70	117/18670	1,98814E-28	1,98814E-28	5,49145E-26	20
GO:1902600	proton transmembrane transport	20/70	163/18670	2,2258E-25	2,2258E-25	3,84243E-23	20
GO:0009060	aerobic respiration	11/70	88/18670	2,30743E-14	2,30743E-14	2,65557E-12	11
Cluster 2							
ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	Count
GO:0007015	actin filament organization	15/46	400/18670	1,98106E-14	1,98106E-14	2,17291E-11	15
GO:0032970	regulation of actin filament-based process	14/46	388/18670	2,91292E-13	2,91292E-13	1,59751E-10	14
GO:0022604	*regulation of cell morphogenesis*	*14/46*	*484/18670*	*5,76941E-12*	*5,76941E-12*	*2,10938E-09*	*14*
GO:0032956	regulation of actin cytoskeleton organization	12/46	343/18670	2,71199E-11	2,71199E-11	7,43657E-09	12
GO:0032535	regulation of cellular component size	12/46	370/18670	6,52232E-11	6,52232E-11	1,43079E-08	12
GO:0110053	regulation of actin filament organization	10/46	261/18670	6,28497E-10	6,28497E-10	1,14894E-07	10
GO:1902903	regulation of supramolecular fiber organization	10/46	353/18670	1,14482E-08	1,14482E-08	1,32556E-06	10
GO:0008154	actin polymerization or depolymerization	9/46	209/18670	1,78846E-09	1,78846E-09	2,80237E-07	9
GO:0008064	regulation of actin polymerization or depolymerization	8/46	179/18670	1,16713E-08	1,16713E-08	1,32556E-06	8
GO:0030832	regulation of actin filament length	8/46	180/18670	1,2192E-08	1,2192E-08	1,32556E-06	8
Cluster 3							
ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	Count
GO:0050900	leukocyte migration	24/126	499/18670	3,24737E-14	3,24737E-14	4,96335E-11	24
GO:0002283	neutrophil activation involved in immune response	22/126	488/18670	1,56874E-12	1,56874E-12	3,45035E-10	22
GO:0042119	neutrophil activation	22/126	498/18670	2,3439E-12	2,3439E-12	3,6623E-10	22
GO:0050867	positive regulation of cell activation	20/126	394/18670	2,0908E-12	2,0908E-12	3,6623E-10	20
GO:0070661	leukocyte proliferation	19/126	298/18670	1,39191E-13	1,39191E-13	1,01383E-10	19
GO:0060326	cell chemotaxis	19/126	304/18670	1,98995E-13	1,98995E-13	1,01383E-10	19
GO:0007159	leukocyte cell-cell adhesion	19/126	337/18670	1,24427E-12	1,24427E-12	3,45035E-10	19
GO:0032943	mononuclear cell proliferation	18/126	274/18670	3,86411E-13	3,86411E-13	1,4765E-10	18
GO:1903039	positive regulation of leukocyte cell-cell adhesion	16/126	218/18670	1,58022E-12	1,58022E-12	3,45035E-10	16
GO:0030595	leukocyte chemotaxis	16/126	224/18670	2,39613E-12	2,39613E-12	3,6623E-10	16
Cluster 4							
ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	Count
GO:0007409	axonogenesis	35/184	468/18670	4,86248E-21	4,86248E-21	1,16034E-17	35
GO:0031589	cell-substrate adhesion	29/184	354/18670	1,34753E-18	1,34753E-18	1,60782E-15	29
GO:0030198	extracellular matrix organization	27/184	368/18670	3,68456E-16	3,68456E-16	2,35214E-13	27
GO:0043062	extracellular structure organization	27/184	369/18670	3,94271E-16	3,94271E-16	2,35214E-13	27
GO:0050673	epithelial cell proliferation	25/184	434/18670	1,18459E-12	1,18459E-12	2,82681E-10	25
GO:0040013	negative regulation of locomotion	24/184	381/18670	5,13638E-13	5,13638E-13	1,53213E-10	24
GO:0051271	negative regulation of cellular component movement	24/184	384/18670	6,08206E-13	6,08206E-13	1,61264E-10	24
GO:0010810	regulation of cell-substrate adhesion	21/184	215/18670	3,04244E-15	3,04244E-15	1,45205E-12	21
GO:0007411	axon guidance	21/184	276/18670	4,33464E-13	4,33464E-13	1,53213E-10	21
GO:0097485	neuron projection guidance	21/184	277/18670	4,65076E-13	4,65076E-13	1,53213E-10	21

Table 4: Statistical analysis

	cluster 1								cluster 3							
	genes	Kruskal-Wallis´s	Dunn´s test			ROC		no-rec x rec	genes	Kruskal-Wallis´s test	Dunn´s test			ROC		no-rec x rec
			GI-GII	GI-GIII	GII-GIII	area	p				GI-GII	GI-GIII	GII-GIII	area	p	
metabolism	*GPI*	0.002	0.003		0.004	0.745	0.001		*EZH2*	0.001	0.001	0.036		0.732	0.002	0.003
	PFKM	0.015	0.004			0.720	0.004		*HLAE*	0.002	0.001			0.746	0.000	0.014
	PGK1	0.018	0.005			0.712	0.005	0.034	*HLAF*	0.047	0.031			0.670	0.014	
	PGAM5	0.004	0.001			0.751	0.001	0.038	*WIPF1*	0.004	0.004			0.713	0.002	0.019
	PDHA1	0.000	0.000			0.799	0.000	0.000	*VAV1*	0.001	0.000			0.747	0.000	
	PDHB	0.023	0.009			0.706	0.007		*HCST*	0.001	0.001	0.028		0.803	0.000	
	PDHX	0.000	0.000			0.795	0.000	0.008	*AIF1*	0.002	0.002			0.737	0.001	
	LDHA	0.043			0.017	0.652	0.046		*TLR5*	0.006	0.002			0.713	0.002	
	LDHB	0.003	0.001			0.759	0.001		*PSTPIP1*	0.007	0.003			0.715	0.002	
	IDH3A	0.000	0.000			0.799	0.000	0.001	*P2RX4*	0.002	0.003		0.022	0.684	0.008	
	OGDHL	0.011	0.005		0.031	0.723	0.003	0.008	*TLN1*	0.004	0.004			0.766	0.000	
	SDHC	0.001	0.000		0.018	0.782	0.000	0.003	*ARRB2*	0.013	0.004			0.695	0.005	
	FH	0.001	0.000			0.772	0.000	0.009	*NCKAP1L*	0.014	0.004			0.695	0.005	
	MDH1	0.003	0.001		0.041	0.759	0.001	0.015	*STK10*	0.011	0.004		0.040	0.651	0.028	
	MTND1	0.000	0.000		0.042	0.814	0.000	0.007	*ITGAM*	0.008	0.005			0.713	0.002	
	MTND2	0.003	0.002		0.009	0.748	0.001		*DOCK2*	0.004	0.005			0.701	0.004	
	MTND3	0.047	0.028		0.048	0.678	0.020	0.020	*EVL*	0.000	0.000		0.021	0.778	0.004	
	MTND4	0.005	0.006		0.005	0.725	0.003		*VSIR*	0.002	0.002			0.781	0.000	
	MTND4L	0.002	0.001			0.761	0.001		*JAML*	0.003	0.003			0.757	0.000	
	MTND5	0.019	0.008		0.049	0.710	0.006		*IL16*	0.005	0.005			0.760	0.000	
	NDUFS1	0.000	0.000		0.002	0.796	0.000		*CSF1R*	0.004	0.006			0.710	0.002	
	NDUFS2	0.024	0.011		0.043	0.703	0.008	0.004	*ARHGAP45*	0.011	0.003			0.686	0.007	
	NDUFV3	0.036	0.018		0.048	0.689	0.013	0.003	*GAPT*	0.015	0.004			0.674	0.013	
	NDUFA1	0.031	0.012			0.697	0.010		*HCLS1*	0.017	0.008			0.697	0.004	
	NDUFA2	0.004	0.001			0.753	0.001	0.036	*SPN*	0.018	0.006			0.689	0.006	
	NDUFA10	0.010	0.006			0.694	0.011		*MPEG1*	0.021	0.007			0.687	0.007	
	NDUFA13	0.019	0.024	0.052		0.654	0.043		*BIN2*	0.025	0.007			0.644	0.036	
	NDUFB3	0.002	0.002		0.005				*TRPM2*	0.026	0.009			0.638	0.045	
	NDUFB4	0.006	0.001			0.744	0.001		*PTPRC*	0.027	0.008			0.677	0.010	
	NDUFB5	0.000	0.000		0.011	0.827	0.000		*WAS*	0.028	0.011			0.682	0.008	
	NDUFB6	0.029	0.01			0.700	0.009		*GPSM3*	0.028	0.009			0.680	0.009	
	NDUFB10	0.016	0.000		0.011	0.694	0.011		*CD74*	0.029	0.010			0.680	0.009	
	NDUFB11	0.020	0.005			0.711	0.006	0.010	*PTAFR*	0.030	0.030			0.680	0.009	
	NDUFC2	0.023	0.001			0.692	0.012	0.033	*RNASE6*	0.030	0.008			0.670	0.014	
	UQCRC2	0.005	0.001			0.750	0.001	0.012	*P2RY12*	0.032	0.015			0.680	0.009	
	MTCO1	0.014	0.006		0.036	0.718	0.004		*IKZF1*	0.039	0.011			0.650	0.029	
	COX4I1	0.042	0.012			0.691	0.012	0.010	*LAIR1*	0.041	0.013			0.666	0.016	
	COX5A	0.002	0.000			0.766	0.000	0.001	*LILRA2*	0.045	0.013			0.654	0.026	
	COX5B	0.001	0.000			0.785	0.000	0.014	*PLCG2*	0.047	0.014			0.644	0.036	
	COX6A1	0.003	0.001			0.728	0.003		*HLAA*	0.143						
	COX6B1	0.001	0.000		0.026	0.797	0.000		*HLAB*	0.396						
	COX6C	0.000	0.000		0.005	0.826	0.000	0.011	*HLAC*	0.714						
	COX7A2L	0.046	0.014			0.689	0.013		*PSMB1*	0.913						
	COX7B	0.006	0.001			0.742	0.001	0.033	*PSMB2*	0.657						
	COX7C	0.005	0.001			0.745	0.001	0.039	*PSMB3*	0.197						
	COX8A	0.008	0.002			0.731	0.002		*PSMB4*	0.179	0.065					0.025
	COX10	0.048	0.03			0.675	0.021	0.032	*PSMB5*	0.115	0.048					
	COX11	0.036	0.01			0.694	0.011		*PSMB6*	0.451						0.039
	COX17	0.004	0.002			0.727	0.003		*PSMB7*	0.910						
	ATP5MC3	0.005	0.001			0.749	0.001	0.037	*PSMB8*	0.104						
	ATP5MG	0.032	0.014			0.695	0.010	0.005	*PSMB9*	0.462						
	ATP5F1B	0.002	0.000			0.764	0.001	0.018	*B2M*	0.741						0.019
	ATP5MPL	0.004	0.002		0.018	0.251	0.001		*TAP1*	0.457						
	ATP5MC1	0.005	0.001			0.748	0.001	0.047	*TAP2*	0.609						
	ATP5PD	0.009	0.002			0.735	0.002	0.010	*LYZ*	0.166	0.065					0.031
	ATP5PF	0.044	0.021			0.665	0.030									
	ATP5PO	0.015	0.004			0.722	0.004	0.010								
	ATPAF2	0.023	0.012			0.701	0.008	0.032								
	GOT1	0.002	0.001			0.772	0.000	0.003								
	GOT2	0.003	0.002			0.727	0.003	0.020								
	GPT2	0.009	0.002			0.735	0.002	0.013								
	H6PD	0.000	0.000		0.036	0.728	0.001	0.013								
	PGD	0.009	0.002			0.698	0.004									
	TFAM	0.040	0.012			0.687	0.014									
	PPARGC1A	0.002	0.002		0.004	0.751	0.001	0.032								
	ESRRA	0.008	0.004			0.703	0.008									
cell cycle	*AURKA*	0.003	0.001			0.744	0.001	0.000								
	CENPF	0.000	0.000	0.042		0.814	0.000	0.000								
	CEP152	0.008	0.004			0.705	0.007	0.000								
	CDK1	0.004	0.003			0.735	0.002	0.000								
	E2F1	0.045	0.040					0.001								
	RECQL4	0.011	0.005			0.713	0.005	0.001								
	TOP2A	0.003	0.001			0.735	0.002	0.001								
	ASPM	0.000	0.000	0.013		0.807	0.000	0.001								
	CABLES2	0.044	0.013			0.685	0.015	0.000								
	SPC24	0.003	0.001			0.739	0.002	0.001								
	AR	0.014	0.004			0.674	0.004	0.005								
	HMGA2	0.032	0.013			0.680	0.019	0.003								
	NUSAP1	0.001	0.000			0.758	0.001	0.003								
	PTTG1	0.000	0.000			0.826	0.000	0.004								
	HMMR	0.000	0.001	0.010		0.728	0.003	0.004								
	NME1	0.002	0.000			0.772	0.000	0.005								
	CHMP4C	0.006	0.009		0.005	0.716	0.005	0.007								
	EGLN3	0.005	0.001			0.747	0.001	0.007								
	UBE2C	0.013	0.006			0.715	0.005	0.007								
	TPX2	0.004	0.002			0.733	0.002	0.008								
	CHMP2A	0.047	0.014			0.685	0.015									
	SLC25A3	0.005	0.001			0.746	0.001									
	CRTAP	0.015	0.007		0.034	0.715	0.005									
organelle mitochondria	*HSPD1*	0.000	0.000	0.039		0.795	0.000	0.001								
	MRPL15	0.000	0.001			0.798	0.000	0.001								
	PPIF	0.002	0.003		0.026	0.772	0.000	0.001								
	HOPX	0.015	0.020	0.044		0.658	0.038	0.002								
	NNT	0.002	0.004			0.763	0.001	0.002								
	CHCHD10	0.009	0.004			0.706	0.007	0.005								
	TOMM20	0.020	0.007			0.699	0.009	0.007								
	TIMM17A	0.001	0.002			0.763	0.001	0.008								
	HSPE1	0.006	0.002			0.731	0.003									
	PDE4D	0.012	0.010		0.012	0.709	0.006									
	UBL5	0.048	0.027		0.049	0.678	0.020									

cluster 2														
genes	Kruskal-Wallis´s	Dunn´s test										ROC		no-rec x rec
		M-T	M-F	M-GII	M-GIII	T-F	T-GII	T-GIII	F-GII	F-GIII	GII-GIII	area	p	
TNNT1	0.001	0.001	0.000						0.020			0.755	0.000	
LIMK2	0.004	0.020	0.019	0.000								0.732	0.001	
BAIAP2	0.003	0.003	0.002	0.012				0.039		0.013		0.729	0.002	
ARHGEF15	0.032	0.030	0.011	0.012								0.693	0.008	
ARHGEF5	0.046	0.010	0.011									0.680	0.013	
PLPPR4	0.029	0.007	0.049					0.036				0.677	0.014	
ARAP3	0.009	0.015	0.016	0.044				0.013		0.009	0.023	0.676	0.015	
ISLR2	0.000	0.002	0.004				0.001		0.002			0.667	0.021	0.018
RHOJ	0.035	0.029	0.006							0.031		0.667	0.021	
HIP1R	0.001	0.002	0.044				0.044	0.001		0.008		0.661	0.026	
TNNI3	0.019	0.001	0.000						0.020			0.686	0.010	
SEMA3D	0.006	0.049	0.000			0.022			0.003	0.024		0.665	0.032	
SPTBN2	0.001	0.009	0.036				0.000		0.003					0.000
PICK1	0.002	0.050		0.000			0.011				0.021			0.009
SPIRE2	0.003	0.020					0.000		0.007					0.007
PARD6B	0.004		0.001			0.024			0.002	0.003				
COBL	0.011						0.007		0.002	0.028				
PPL	0.013	0.003					0.012							
MARK1	0.014		0.050		0.026				0.008		0.005			0.032
TRIOBP	0.026			0.001			0.030							0.029
FSTL4	0.030	0.049	0.016				0.048		0.015					
GAS2	0.030		0.012						0.005	0.020				

cluster 4														
genes	Kruskal-Wallis´s	Dunn´s test										ROC		no-rec x rec
		M-T	M-F	M-GII	M-GIII	T-F	T-GII	T-GIII	F-GII	F-GIII	GII-GIII	area	p	
AR	0.001	0.037	0.004				0.003		0.000			0.759	0.008	0.004
MN1	0.000		0.014		0.034		0.002	0.002	0.000	0.000		0.784	0.000	0.000
CYP1B1	0.000		0.001	0.03		0.01	0.000		0.000	0.004		0.783	0.000	0.000
IGFBP5	0.000		0.012	0.003			0.000		0.000	0.016		0.810	0.000	0.000
ENG	0.018						0.002		0.008			0.711	0.002	0.000
SFRP1	0.000		0.007			0.042	0.004	0.020	0.000	0.001		0.811	0.001	0.000
PODN	0.008		0.015				0.029		0.001	0.008		0.773	0.005	0.002
EMILIN1	0.009						0.004		0.000			0.687	0.007	0.000
PTPRU	0.000		0.028	0.045	0.005	0.049	0.006	0.001	0.000	0.000		0.791	0.000	0.003
MMP28	0.013		0.018				0.018		0.001			0.757	0.008	0.000
GDF10	0.001		0.001			0.003			0.000	0.001		0.865	0.000	0.001
TGFB3	0.011		0.007			0.033	0.044		0.001	0.027		0.788	0.003	0.001
LTBP1	0.004		0.001			0.045			0.002	0.011		0.796	0.002	0.001
FGL2	0.000	0.015	0.000			0.049		0.002	0.002	0.000		0.817	0.001	0.005
ZEB1	0.009		0.033				0.004		0.002			0.712	0.029	0.020
AEBP1	0.000		0.002			0.033	0.001		0.000	0.016		0.827	0.001	0.001
COL8A2	0.000		0.002				0.006	0.005	0.000	0.000		0.802	0.002	0.004
NTN1	0.000	0.043	0.003		0.037	0.048	0.006	0.001	0.000	0.000		0.831	0.000	0.009
MATN2	0.001		0.000			0.010	0.044		0.000	0.005		0.849	0.000	0.030
NTN4	0.001		0.004			0.019	0.023		0.000	0.000		0.828	0.001	0.031
EGFL6	0.000	0.008	0.000			0.033	0.009	0.043	0.000	0.001		0.843	0.000	0.032
LTBP2	0.003		0.001			0.050	0.022		0.001	0.025		0.796	0.002	0.007
COL8A1	0.005		0.000			0.008			0.001	0.009		0.838	0.001	0.014
CDH23	0.000		0.002			0.041	0.000		0.000	0.008		0.825	0.001	0.000
SMOC2	0.000		0.002				0.000	0.023	0.000	0.003		0.789	0.003	0.001
ROM1	0.002		0.008			0.030	0.019		0.000		0.007	0.775	0.005	0.002
SSPN	0.000		0.040	0.003			0.000		0.000		0.008	0.759	0.008	0.000
SULF2	0.001			0.024	0.067		0.001	0.013	0.001	0.007				0.000
ATXN3	0.001			0.002			0.000				0.002			0.000
ARID5B	0.002			0.020			0.001		0.000		0.004	0.701	0.039	0.000
HEXIM1	0.018						0.005		0.002			0.694	0.046	0.000
ZRANB1	0.018						0.005		0.004					0.000
TCF7L2	0.019			0.006			0.024		0.003					0.000
PLCE1	0.003		0.017				0.005		0.001	0.013		0.743	0.012	0.001
CDC42BPB	0.006						0.002		0.002		0.021			0.001
TRIP11	0.013						0.011		0.002		0.020			0.001
ANK3	0.040						0.016		0.007					0.001
CDH5	0.006						0.003		0.001			0.721	0.023	0.002
DAAM1	0.002			0.000			0.001		0.023		0.010			0.002
BMPR1A	0.001	0.034					0.003	0.004	0.011	0.006				0.003
ARHGAP21	0.006						0.007	0.008	0.016	0.009				0.003
FXYD5	0.001		0.007					0.002	0.006	0.000		0.760	0.007	0.004
NUMB	0.012			0.011			0.001				0.012			0.004
PLCB1	0.002	0.021	0.002					0.012	0.007	0.001		0.762	0.007	0.005
DOCK1	0.013						0.004		0.002			0.702	0.037	0.005
PSEN1	0.000			0.000			0.000		0.045					0.005
JCAD	0.002			0.002	0.012		0.011	0.038	0.003	0.009				0.006
MFAP4	0.012		0.008						0.005	0.004		0.760	0.007	0.008
VAT1	0.004		0.038		0.043		0.042	0.008	0.004	0.001		0.744	0.012	0.011
PBLD	0.046			0.003			0.033							0.024
TRIM8	0.000			0.013			0.000	0.028	0.001					0.028
SFRP2	0.002		0.001						0.004	0.003		0.790	0.003	0.041
MBP	0.006	0.019					0.017	0.004		0,021				0.042
ROCK1	0.013			0.040		0.028			0.001		0.033	0.742	0.013	0.043
THSD4	0.000		0.001				0.011	0.002	0.002	0.000		0.778	0.004	0.045
SERPINF1	0.009		0.003			0.014			0.000	0.027		0.812	0.001	
FBLN1	0.002		0.000			0.010			0.001	0.006		0.843	0.000	
NKD1	0.001	0.032	0.001			0.036		0.015	0.003	0.000		0.811	0.001	
ELN	0.000		0.000				0.020	0.009	0.001	0.001		0.795	0.002	
MFGE8	0.021		0.007			0.046			0.002	0.021		0.773	0.005	
COL1A2	0.009		0.001						0.006			0.767	0.006	
PODNL1	0.014		0.003						0.016	0.005		0.764	0.007	
SORBS3	0.000		0.033		0.048		0.004	0.008	0.000	0.001		0.764	0.007	
EXT1	0.000	0.003	0.002					0.000	0.040	0.000	0.011	0.753	0.009	
COL26A1	0.021		0.006						0.040	0.008		0.732	0.017	
TPM1	0.012						0.012		0.003	0.015		0.715	0.027	
MYH10	0.004	0.015	0.029				0.009	0.015	0.019	0.016				
FZD4	0.006	0.012					0.007	0.018	0.044	0,040				

Análise crítica

Meningiomas atípicos e recorrentes apresentaram aumento do metabolismo oxidativo e divisão celular

As células tumorais requerem alta energia e substratos para crescer e se dividir, além de precisarem controlar o potencial redox e as espécies reativas de oxigênio (ROS) para sobreviver. Os níveis de todos esses metabólitos estabelecem a bioassinatura do que se denomina agressividade metabólica (144). De fato, a nossa análise transcriptômica dos meningiomas de diferentes graus revelou uma reprogramação metabólica com aumento da expressão gênica particularmente dos genes relacionados à fosforilação oxidativa (OXPHOS), incluindo a hiperexpressão de genes mitocondriais e nucleares que codificam proteínas do complexo I a V da cadeia respiratória nos meningiomas atípicos (MA-GII) em comparação com os benignos (GI). Consistente com este aumento do metabolismo oxidativo mitocondrial, uma regulação positiva de um conjunto de genes relacionados ao tráfego de proteínas para as mitocôndrias e síntese de proteínas mitocondriais foi detectada em MA-GII, com expressão significativamente mais elevada em meningiomas recorrentes. Além disso, a regulação positiva de genes relacionados a OXPHOS demonstrou-se estar fortemente correlacionada com a regulação positiva do coativador 1 alfa do receptor gama ativado de proliferação peroxissomal (*PPARGC1A*, também conhecido como *PGC1α*) e do receptor alfa relacionado ao estrogênio (*ESRRA*). ESRRA é um receptor nuclear único e efetor do PCG1α, que regula a expressão de genes envolvidos em OXPHOS e biogênese mitocondrial. A expressão de PGC1α foi significativamente maior em MA-GII em comparação com GI e particularmente maior em meningiomas recorrentes em comparação com não recorrentes, corroborando relatos anteriores de sua regulação positiva em células tumorais proliferativas aumentando a capacidade respiratória mitocondrial (144, 145). Curiosamente, uma co-expressão significativa das subunidades dos complexos OXPHOS foi observada em paralelo à hiperexpressão de *ESRRA* em MA-GII em relação ao GI. A significativa hiperexpressão do principal regulador da replicação/transcrição do DNA mitocondrial, o fator de transcrição mitocondrial A (*TFAM*), observada em MA-GII também foi convergente para o papel do PGC1α na biogênese mitocondrial (146). No entanto, as correlações de expressão entre os genes OXPHOS codificados pelos genomas mitocondrial e nuclear

detectados no GI foram perdidos no MA-GII, sugerindo um desacoplamento da cadeia de transporte de elétrons com a produção de espécies reativas de oxigênio (ROS). ROS medeiam a interação entre os genes reguladores e metabólitos, e modulam várias vias de sinalização oncogênica (147), que culmina na proliferação de células tumorais. De fato, as expressões de vários genes relacionados à divisão celular, particularmente relacionados à regulação da transição G2/M da mitose, sob a modulação do fator de transcrição E2F1, mostraram-se reguladas positivamente em MA-GII e principalmente em meningiomas recorrentes. Além disso, uma ativação do eixo E2F1-EZH2 foi detectada em meningiomas recorrentes, convergente a relatos anteriores relacionando a ativação deste eixo à agressividade do tumor (148, 149). De fato, EZH2, uma subunidade catalítica cardinal do complexo repressivo polycomb 2 (PRC2), um complexo que promove o silenciamento da transcrição por metilação da lisina 27 da histona 3 (H3K27), demonstrou modular a via de sinalização do ciclo celular pelo E2F, sendo este necessário para a expressão dos genes relacionados à proliferação induzidas por E2F (150). Digno de nota, a hiperexpressão de EZH2 discriminou fortemente MA-GII de GI e sua expressão foi significativamente maior em meningiomas recorrentes. Um estudo recente de interesse apontou que a hiperexpressão concomitante de EZH2 e TOP2A permitiu uma estratificação de risco de agressividade em câncer de próstata e abriu uma oportunidade para abordagem terapêutica combinada contra estes dois alvos (151). Considerando-se a presença da hiperexpressão significativa desses genes também em meningiomas GII e particularmente em tumores recorrentes, uma terapia combinatória direcionada a EZH2 (152) e a genes relacionados à divisão celular como TOP2A seria uma terapêutica alternativa para os meningiomas agressivos.

Meningiomas atípicos e recorrentes apresentaram evasão imunológica desencadeada pelo aumento da expressão de EZH2

As células cancerosas proliferam evitando os sistemas imunes inato e adaptativo. Antígenos tumorais estranhos devem ser apresentados à superfície das células tumorais ligadas às moléculas principais de histocompatibilidade classe I (MHC-I) para serem reconhecidas por células T citotóxicas $CD8^+$ para sua eliminação. Qualquer supressão do sistema MHC-I pode fornecer vantagem às células cancerosas. O processo da

apresentação do antígeno pela via do MHC-I envolve várias etapas, incluindo componentes de imunoproteassoma (PSMBs), transportadores de peptídeos associados ao processamento de antígenos (TAP1, TAP2), estabilizador de estrutura (B2M) e moléculas de cadeia pesada MHC-I (HLAs), que afloram peptídeos intracelulares à superfície celular para o reconhecimento de células T $CD8^+$. Um estudo muito recente identificou um papel essencial para PCR2 na repressão transcricional dos genes da via do MHC-I modulada por EZH2. Convergente a este dado publicado, nós também identificamos um baixo nível de expressão dos genes relacionados ao MHC-I, especialmente a *HLA-E* e *HLA-F,* que se correlacionaram inversamente ao nível de expressão do *EZH2* nos meningiomas GII e tumores recorrentes. Este achado sugeriu a presença de diminuição da vigilância imunológica em tumores recorrentes. Além disso, encontramos hipoexpressão concomitante de vários outros componentes de processos imunológicos, que também se correlacionaram negativamente com *EZH2* como genes relacionados a: a) formação de sinapses imunológicas correspondendo a movimentos moleculares por meio da remodelação do citoesqueleto de actina (*NCKAP1L* (153), *DOCK2* (154)); b) proteínas adaptadoras citosólicas envolvidas na ativação de células imunes (*HCST* (155), *PSTPIP1* (156)*, AIF1* (157)*, P2RX4* (158)); c) sinalização de dentro para fora para ativação de células T através da estimulação de integrinas (*VAV1* (159)); d) regulador de resposta do interferon tipo I (*ARRB2* (160)) modulador de adesão e migração de leucócitos (*ITGAM* (161)).

Adicionalmente, observamos a diminuição da expressão do gene *WIPF1* que codifica a proteína WIP associada à imunodeficiência(162) em GII, principalmente em meningiomas recorrentes.

Meningiomas meningoteliais apresentaram regulação positiva de genes relacionados à reorganização do citoesqueleto de actina e expressão da proteína EZH2 citosólica.

Estudos anteriores em células T e fibroblastos descreveram a existência de uma atividade metiltransferase do complexo EZH2 cataliticamente ativa no citosol relacionada à polimerização da actina, que é dependente da atividade de pequenas GTPases (163). Curiosamente, a hiperexpressão significativa de vários genes associados à reorganização do citoesqueleto de actina foi observada em meningiomas meningoteliais, incluindo *LIMK2, BAIAP2, ARGHGEP5, ARGHGEP15, ARAP3, RHOJ*,

que estão associados a pequenas proteínas GRho. Esses genes codificam proteínas envolvidas com lamelipódios, filipódios, fibras de estresse, formação de adesão focal e regulação da forma celular. EZH2 foi descrito como operando a montante das GTPases e controlando o sinal gerados entre os receptores da membrana plasmática e GTPases (164). Notavelmente, encontramos distribuição citosólica de EZH2 principalmente em meningiomas meningoteliais.

Meningiomas fibrosos apresentaram regulação positiva de genes relacionados à remodelação da matriz extracelular

Observamos a regulação positiva significativa de vários genes que codificam proteínas que remodelam a matriz extracelular (MEC) para uma rede proteica mais densa em meningiomas fibrosos. Identificamos genes que codificam para colágeno fibrilar (*COL1A2*), componente macromolecular do subendotélio (*COL8A1/2*); fibulina associada à membrana basal e fibras elásticas (*FBLN1*); elastina (ELN); matrilina envolvida na formação da rede filamentosa (*MATN2*); proteína secretada semelhante ao fibrinogênio (*FGL2*) e netrina da família de proteínas secretadas relacionadas à laminina (*NTN1/4*). Além disso, encontramos a regulação positiva de genes relacionados ao fator-beta de crescimento transformador (*TGFβ*) que estimulam a síntese de componentes da MEC. Entre eles, observamos a regulação positiva da codificação de *TGFB3*, um ligante que se liga aos receptores *TGFβ* para recrutar e ativar fatores de transcrição da família SMAD; *GDF10* (fator de diferenciação de crescimento 10) que codifica um ligante secretado de TGFβ; e *LTBP1/2* (proteína de ligação ao fator de transformação de crescimento latente 1 e 2) envolvidas na estrutura da MEC e regulam a biodisponibilidade de membros da família TGFβ e sua ativação mediada por integrina. Também observamos a regulação positiva de genes que modulam a angiogênese, como *SERPINF1* (membro 1 da família F de serpinas) que codifica para uma proteína secretada que inibe fortemente a angiogênese. O *NTN4* também está envolvido na angiogênese e na adesão de células murais às células endoteliais; e *EGFL6* (domínio semelhante ao EGF múltiplo 6) regula a angiogênese e a interação epitélio-mesênquima. Curiosamente, a hiperexpressão de *EGFL6* foi relatada anteriormente em meningioma benigno, como candidato envolvido na patogênese do meningioma fibroso através da modulação do ciclo celular via PI3K/Akt e das vias de TGFβ (165). A expressão de *EGFL6* apresentou

o maior escore para discriminar meningioma fibroso (AUC = 0,843, p = 0,001) entre os demais tipos histológicos de meningiomas em nossa coorte, corroborando o relato anterior.

Notavelmente, o nível de expressão de *AR* (receptor de andrógeno) também discriminou meningioma fibroso (AUC = 0,759, p = 0,008) e se correlacionou negativamente com a expressão de *EZH2* entre meningiomas GI (r = -0,312, p = 0,005). O nível de expressão mais alto de *AR* no meningioma fibroso em nossa coorte pode não ser devido à ocupação direta de seu promotor por EZH2, como descrito anteriormente no câncer de próstata (166), mas pode ser o resultado da regulação recíproca com *ZEB1* (*zinc-finger E-box binding homeobox 1*) como previamente descrito em câncer de mama (167). *ZEB1* é um fator de transcrição que desempenha um papel importante na regulação da transição epitélio-mesênquima (EMT), e sua ativação está correlacionada com desdiferenciação epitelial (168). Por outro lado, *ZEB1* pode ser ativada por citocinas como TGFβ, estreitamente correlacionado à expressão de genes de colágeno (169).

Genes relacionados à organização do citoesqueleto de actina e remodelamento da matriz extracelular apresentam-se hipoexpressos em meningiomas atípicos e recorrentes

A análise do transcriptoma de 91 meningiomas aliados aos dados de segmento clínico de pelo menos 5 anos destes pacientes quanto a sobrevida livre de doença (DFS), i.e, recorrência do tumor e ao tempo de sobrevida total (OS) revelou um grupo de genes com escores significativos na predição destes parâmetros clínicos. Entre eles destacaram-se os genes relacionados à reorganização do citoesqueleto de actina, da adesão celular e da regulação negativa da migração que se apresentaram hipoexpressos em MA-GII, consistentes com a característica invasiva destes meningiomas. Dentre eles, a hipoexpressão de *CYP1B1*, identificado como um gene envolvido na motilidade celular, atribuiu menor sobrevida global (OS) e tempo livre de doença (DFS) mais curto aos MA-GII. Curiosamente, o gene meningioma 1 (MN1) também foi identificado como um dos 5 principais genes preditores da evolução clínica. *MN1* está localizado no cromossomo 22q12.1 próximo ao gene *NF2* (Chr 22q12.2) e funciona como um coativador da transcrição. Sugere-se que a inativação desse gene contribui para a patogenia do

meningioma(170). A hiperexpressão de *MN1* conferiu melhor evolução clínica aos pacientes com meningiomas.

Em contraste, a hiperexpressão dos genes *CENPF*, *HMMR* e *TOP2A*, relacionados ao ciclo celular identificados no cluster 1, apresentaram escores significativos na predição de OS e DFS mais curtos em comparação aos que apresentaram hipoexpressão destes genes.

CENPF, *centromere protein F*, codifica uma proteína associada com o complexo centrômero-cinetocore, sendo um componente da matriz nuclear durante a interfase G2, e desempenha a função de segregação do cromossomo durante a mitose. *CENPF* foi identificado como um marcador de proliferação celular em vários cânceres, incluindo câncer de mama (171), carcinoma hepatocelular (CHC) (172) e outros tumores (173). Foi mostrado recentemente que *CENPF* e *FOXM1* são reguladores sinérgicos de malignidade do câncer de próstata e são indicadores prognósticos de baixa sobrevida e metástase (174).

HMMR, *hyaluronan mediated motility receptor*, codifica uma proteína intracelular associada a microtúbulos, sendo um fator agregador de fusos, que localiza complexos proteicos para aumentar a atividade de kinases mitóticas, como *polo-like kinase1*e *aurora kinase A* e controla as atividades de dineinas e kinesinas (175). A expressão de *HMMR* é regulada pelo ciclo celular com pico de expressão entre a fase G2 tardia e mitose precoce (176). De forma consistente, a expressão de *HMMR* é baixa na maioria dos tecidos saudáveis, mas é elevada em tecidos proliferativos, como testículos, baço, placenta e timo (177, 178). Além disso, a expressão elevada de HMMR está associada a um mau prognóstico em uma variedade de cânceres, como: colo-retal (179), mama (180), estômago (181), endometrial (182), próstata (183) e mieloma múltiplo (184).

TOP2A, *DNA topoisomerase II alpha,* codifica uma enzima nuclear que controla os estados topológicos do DNA durante a transcrição, estando envolvida na condensação de cromossoma, separação de cromátide e no alívio do estresse de torsão durante a transcrição e replicação do DNA (185). TOP2A tem sido descrito em vários tipos de câncer como de mama, ovário e próstata estando associado à proliferação tumoral e invasividade no câncer mamário (186) e à regulação epigenética através do EZH2 no

câncer de próstata (187). Adicionalmente, TOP2A foi associado à resistência aos medicamentos no câncer de cólon (188).

CONCLUSÕES

- Grau histológico foi o fator mais importante na determinação do tempo de sobrevida a longo prazo em pacientes com meningioma. A recorrência não apresentou impacto substancial na mortalidade ou no estado neurológico em pacientes com meningioma GI, mas todos os pacientes com GII ou GIII que apresentaram recorrência tumoral, morreram devido ao tumor. Assim, a ressecção completa do meningioma é desejável, mas deve ser cuidadosamente ponderada contra novas morbidades nos pacientes com meningioma GI. Para pacientes com meningiomas GII e GIII, a ressecção total do tumor foi o fator que determinou a melhor chance de sobrevida a longo prazo.

- Após análises de revisões da literatura sobre o impacto da faixa etária, da localização, bem como da apresentação clínica chegamos as seguintes conclusões: (i) a faixa etária juvenil (abaixo de 20 anos) não impactou na taxa de recorrência tumoral, diferindo da apresentação clínica das outras faixas etárias, pelo maior número de pacientes do sexo masculino e de uma prevalência maior de meningiomas atípicos; (ii) as localizações ventriculares bem como tumores espinhais não impactaram na recorrência nem na taxa de sobrevida dos doentes, diferindo apenas no subtipo mais prevalente, sendo os fibrosos mais frequentes nos ventrículos e os psamomatosos mais frequentes na coluna vertebral; (iii) a apresentação clínica com multiplicidade tumoral bem como hemorragia tumoral não impactaram a taxa de recorrência ou sobrevida total.

- A cirurgia ainda é a principal forma de tratamento para meningiomas GII, com maior impacto para prolongar o tempo de sobrevida. Embora a indicação da RT ainda seja uma questão controversa em meningiomas, a análise da nossa casuística demonstrou ser esta uma terapia adjuvante com impacto positivo quanto ao tempo de sobrevida livre de progressão tumoral. A revisão sistemática sobre radioterapia (RT) e seu impacto na recorrência dos meningiomas atípicos não evidenciou que a RT tenha diminuído a taxa de recorrência naqueles pacientes. No entanto, observou-se critérios não uniformes na indicação da RT. Estudos prospectivos com uniformidade de protocolos serão necessários para avaliar o impacto da RT na recorrência dos meningiomas atípicos.

- A revisão dos aspectos moleculares em meningiomas mostrou uma baixa frequência de mutações somáticas, diferindo de outros tumores sólidos com alta incidência de mutações em genes "*drivers*" de oncogênese. Meningiomas são, portanto, tumores considerados com "quiet genome", onde outros mecanismos moleculares deverão ser preponderantes na tumorigênese, como modificações epigenéticas.

- A análise transcriptômica da nossa coorte de meningiomas identificou um conjunto de genes diferencialmente expressos em GII relacionado à ativação do metabolismo oxidativo associado ao aumento da divisão celular, à evasão imune e à regulação da motilidade levando ao aumento da migração. Os níveis de expressão de vários genes foram preditivos de progressão tumoral, em particular os genes relacionados ao ciclo celular e à remodelamento da matriz extracelular, sendo potenciais candidatos para monitorar a evolução destes tumores e alvos terapêuticos para futuras terapias adjuvantes.

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ANEXOS

USP - FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO - FMUSP

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: IDENTIFICAÇÃO DE MARCADORES TUMORAIS IMPLICADOS NA RECORRÊNCIA TUMORAL DOS MENINGIOMAS ATÍPICOS

Pesquisador: Suely Kazue Nagahashi Marie

Área Temática: Genética Humana:
(Trata-se de pesquisa envolvendo Genética Humana que não necessita de análise ética por parte da CONEP;);

Versão: 3

CAAE: 63079616.2.0000.0065

Instituição Proponente: Hospital das Clínicas da Faculdade de Medicina da USP

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.135.672

Apresentação do Projeto:

IDENTIFICAÇÃO DE MARCADORES TUMORAIS IMPLICADOS NA RECORRÊNCIA TUMORAL DOS MENINGIOMAS ATÍPICOS

Objetivo da Pesquisa:

identificação de marcadores tumorais especificos em meningiomas atipicos que evoluem mal

Avaliação dos Riscos e Benefícios:

não há risco - estudo histoquimico e anatomopatologico

benefício - previsão de evolução mais desfavoravel em alguns tipos tumorais

Comentários e Considerações sobre a Pesquisa:

o n da amostra é pequeno, dada a especificidade do estudo em questão

estudo com finalidade de conclusão de doutoramento

Considerações sobre os Termos de apresentação obrigatória:

adequados

Recomendações:

não há

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Conclusões ou Pendências e Lista de Inadequações:

ndn

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1272680_E1.pdf	06/12/2018 22:22:45		Aceito
Outros	CRONOGRAMA_2018.docx	06/12/2018 22:20:28	Suely Kazue Nagahashi Marie	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	JUSTIFICATIVADADISPENSADOTCLE.docx	02/02/2017 22:49:23	Suely Kazue Nagahashi Marie	Aceito
Outros	USP.pdf	15/12/2016 19:46:12	Suely Kazue Nagahashi Marie	Aceito
Folha de Rosto	FOLHADEROSTO.pdf	15/12/2016 19:43:12	Suely Kazue Nagahashi Marie	Aceito
Projeto Detalhado / Brochura Investigador	TESEDR.doc	24/10/2016 14:06:22	Suely Kazue Nagahashi Marie	Aceito
Cronograma	CRONOGRAMA.docx	24/10/2016 14:00:54	Suely Kazue Nagahashi Marie	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

SAO PAULO, 07 de Fevereiro de 2019

Assinado por:
Maria Aparecida Azevedo Koike Folgueira
(Coordenador(a))

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