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Multiple meningiomas: Epidemiology, management, and outcomes

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Abstract

Meningiomas are the most common nonmalignant brain tumor in adults, with an increasing incidence of asymptomatic meningiomas diagnosed on more ubiquitous neuroimaging. A subset of meningioma patients bear 2 or more spatially separated synchronous or metachronous tumors termed "multiple meningiomas" (MM), reported to occur in only 1%–10% of patients, though recent data indicate higher incidence. MM constitute a distinct clinical entity, with unique etiologies including sporadic, familial and radiation-induced, and pose special management challenges. While the pathophysiology of MM is not established, theories include independent origin in disparate locations through unique genetic events, and the "monoclonal hypothesis" of a transformed neoplastic clone with subarachnoid seeding precipitating numerous distinct meningiomas. Patients with solitary meningiomas carry the risk of long-term neurological morbidity and mortality, as well as impaired health-related quality of life, despite being a generally benign and surgically curable tumor. For patients with MM, the situation is even less favorable. MM should be regarded as a chronic disease, and in many cases, the management goal is disease control, as cure is seldom possible. Multiple interventions and lifelong surveillance are sometimes necessary. We aim to review the MM literature and create a comprehensive overview, including an evidence-based management paradigm.

Key Points

- Given high disease burden, MM treatment should focus on disease control, not cure.
- Management of MM may involve observation, surgery, and radiosurgery.
- Evidence for gold-standard care in MM is limited, requiring further research.

Meningioma is the most common nonmalignant brain tumor in adults and accounts for 38% of all brain tumors and 55% of nonmalignant primary brain tumors.[1] With the recent extensive use of neuroimaging, the incidence of meningiomas has increased and is estimated to occur in up to 1% of the population.[2] Meningiomas are typically slow growing, and the vast majority remain asymptomatic, thus, 50% are diagnosed at autopsy.[3–5] The increasing numbers of asymptomatic meningiomas diagnosed on neuroimaging demands further development of treatment and follow-up strategies.[6]

Multiple meningiomas (MM), also known as meningiomatosis, have generally been reported to occur in only 1%–10% of patients with meningiomas,[7–10] but a more recent study indicates that the incidence is higher than previously thought.[11] There is no standardized definition of MM, but it is generally agreed as ≥2 spatially separated synchronous or metachronous lesions.[8,10–15] The first case of MM was reported by Anfimow and Blumenau in 1889[11] and the first attempt to define MM as a distinct entity was made by Cushing and Eisenhardt (1938) as "more than one and less than a diffusion

Importance of Study

With the rising incidence of meningiomas and the ubiquity of cross-sectional neuroimaging, more patients with multiple meningiomas (MM) are being identified. These patients have a higher disease burden, with limited possibility of cure, requiring multiple interventions, and demonstrating potentially worse neurological and functional outcomes. This study provides an up-to-date understanding of MM epidemiology and etiology, including a current understanding of meningioma genetics and molecular biology, and exploring current research detailing the management and outcomes of MM. We outline management perspectives to MM, including a chronic disease model of care framework, with approaches including observation, radiotherapy, and surgery. We further provide current evidence on outcomes following intervention. To the best of our knowledge, this is the first attempt to develop evidence-based guidelines for the management of MM.

in the absence of stigmata of von Recklinghausen's disease."[16] The aim of this distinction was to differentiate sporadic MM as a condition separate from that seen in association with neurofibromatosis type 1 (NF1, von Recklinghausen's disease).[12,13] Their definition is problematic, in particular, in the light of the Manchester criteria for clinical diagnosis of neurofibromatosis type 2 (NF2), which includes the presence of MM.[17] Nonetheless, patients with NF2 are often excluded from studies on MM.[8,10–15] The importance of making a distinction between MM and diffuse primary tumors of the meninges, such as diffuse meningiomatosis, was recommended a few decades ago but is seldom mentioned in more recent publications.[12,16] In future studies, a more precise definition of MM is warranted. A deficit of the current definition is that "spatially separated" is vague and open to interpretation; additionally, "metachronous" is problematic to differentiate tumor recurrence in the same location after surgical resection rather than MM.

It is well-established that MM represents a heterogeneous group of conditions with different etiologies and constitutes a distinct clinical entity posing special management challenges. They can be sporadic, hereditary, or radiation-induced. Familial cases of MM can be attributed to numerous inherited cancer syndromes with germline mutations in genes thought to be related to meningioma initiation and progression (shown in parentheses), including NF2 (*NF2*), Cowden syndrome (*PTEN*), Gorlin syndrome (*PTCH1*, *SUFU*), Werner Syndrome (*LMNA*), Li Fraumeni syndrome (*TP53/CHEK2*), von Hippel–Lindau syndrome (*VHL*), and Multiple Endocrine Neoplasia type I (*MEN1*).[18] Radiation-induced meningiomas (RIM) are the most common radiation-induced neoplasm[19–21] and in the absence of a familial syndrome the presence of multiple lesions is suggestive of RIM.[22]

The pathophysiology of MM is not clear, but there are 2 dominant theories. The first is that these tumors occur independently, are isolated sporadic neoplasms, driven by different key genetic events, arising in different locations. This hypothesis is supported by histologic and cytogenetic differences observed between different meningiomas in a single patient.[10,13,15,23–28] Conversely, the monoclonal hypothesis proposes that MM originates from a single neoplastic transformed clone that subsequently spreads along the meninges to form multiple monoclonal meningiomas. This hypothesis is supported by the fact that most MM present the same histological features and molecular genetic analyses, including detection of a common *NF2* gene mutation that strongly favors a monoclonal origin.[4,13,25,27–32] There is evidence that both theories might be true and applicable to different patients.[8]

Patients with solitary meningiomas (SM) carry the risk of long-term neurological morbidity and mortality, as well as impaired health-related quality of life (HRQoL) compared to healthy controls, despite being a largely benign and curable tumor.[33–37] For patients with MM, the situation is even less favorable. MM should be regarded as a chronic disease, and in many cases, the management goal is disease control as a cure is seldom feasible. Multiple interventions and lifelong surveillance are sometimes necessary. We aim to review the MM literature and create a comprehensive overview, including an evidence-based management paradigm.

Methods

We conducted a PubMed search up to 27 December 2021 using the term "multiple meningiomas" which returned 319 articles. Articles without or incomplete abstracts, not written in English, and case reports were excluded. The remaining 107 articles were reviewed. Additional references were obtained from the literature. There were no limitations regarding publication date or exclusion criteria for this narrative review.

Epidemiology

Epidemiological data on MM is rare and mostly limited to case reports and small case series.[7,8,10] There is one recently-published large study, using data from the surveillance, epidemiology, and end results (SEER) program, which provides important epidemiological data on MM. This included patients aged >18 years with intracranial

meningioma from 1975 to 2017, excluding those with neurofibromatosis or retinoblastoma.[11]

Incidence

Traditionally, the incidence of MM has been reported to be between 1% and 3%, based on 8 classical series with a total of 1769 cases.[12,13] After the introduction of computed tomography (CT), the number of imaging verified, but asymptomatic, cases increased. In the early CT era, Lusins et al (1981) reported a MM incidence of 8.9% in a series of 168 cases of meningioma studied by CT, and during the same year, Nahser et al (1981) reported an incidence of 5.9% in a cohort of 84 patients.[12,13] In the absence of larger studies, MM were most often reported in 1%–10% of patients.[7–10] However, in a recent multicenter study of 838 patients with meningioma, 11.46% had more than 1 lesion,[38] and in the previously mentioned SEER study of 99 918 patients with meningiomas, 81 253 (82%) had SM, whereas 18 665 (19%) patients had 2 or more lesions.[11] Thus, the true incidence is likely much higher than previously thought.[11] However, this is not the first report of a higher incidence; Wood et al (1957) found an incidence of MM of 16% in their review of 100 intracranial meningiomas found incidentally at necropsy.[39]

The number of meningiomas per patient varies in the literature. The reported mean number of meningiomas per patient varies, with the SEER study reporting 2.2 per patient and Tsermoulas et al (2018) reporting 3.4 per patient, with a 2019 systematic review reporting 3.1 per patient.[8,10,11] Those with RIM tend to have significantly more tumors than sporadic multiple meningiomas patients.[8,21] Ultimately, the number of meningiomas tends to follow a negative exponential curve, observed in both the SEER study and Tsermoulas et al (2018) (Table 1).[8,11]

While World Health Organization (WHO) grading of meningiomas between study populations varies, no study shows a difference in WHO grades between MM and SM.[8–11,40,41] The Central Brain Tumor Registry of the United States (CBTRUS) 2013–2017 data reports that among 81.3% of reported meningiomas with grading, 80.3% of newly diagnosed meningiomas are WHO grade 1, 17.9% WHO grade 2, and 1.6% WHO grade 3.[1] These numbers differ from those reported by the SEER study and Tsermoulas et al (2018), which note a relative overrepresentation of WHO grades 2 and 3 tumors in comparison (Table 1). Interestingly, grading was not significantly different between RIM and sporadic cases, in agreement with previous studies.[8,21]

Demographics

The incidence of meningioma increases with advancing age, with meningiomas most common in adults aged ≥65 years old and relatively uncommon in children aged 0–14 years old, with a median age at diagnosis of 66 years.[1] The SEER study demonstrated a significantly older cohort of MM patients (median 71 years old) compared to SM patients (median 64 years), though other authors

Table 1. Multiple meningioma proportions and demographics

	Study		
	Tsermoulas et al[8]	Pereira et al[10]	Ramos-Fresnedo et al[11]
n	133	21	18 665
Age (years)	58	55.8	71*
Sex (female:male)	3.6:1	3.2:1	2.3:1
Tumor number			
2	60 (46.6)	-	15 444 (82.7)
3	33 (24.8)	-	2615 (14.0)
4	12 (9.02)	-	473 (2.53)
5	12 (9.02)	-	89 (0.48)
6	3 (2.25)	-	28 (0.15)
7	7 (5.26)	-	11 (0.05)
8	2 (1.50)	-	4 (0.02)
≥9	4 (3.00)	-	2 (0.01)
Tumors per patient	3.4	2.8	2.2
WHO grade			
Grade 1	68 (51.1)	20 (95.2)	17 629 (91.9)
Grade 2	19 (14.3)	1 (4.76)	679 (3.64)
Grade 3	3 (2.25)	-	357 (1.91)

The reported proportion of multiple meningiomas according to key variables. Age is reported as mean age in years, excepting (*), which is a reported median age. Figures are listed as gross numbers, with percentages of total in parentheses.[8,10,11]

report a lower mean age at diagnosis for MM patients of 53.7–58 years, often not significantly different from SM patients (Table 1).[8,10,11,38] MM are rare in childhood and adolescence.[42]

Sex distribution of meningioma is known to be asymmetrical, with women at increased risk of meningioma. WHO grade 1 meningioma is overall 2.3 times more common in women compared to men, with the greatest risk differential of 3.29 between 35 and 54 years of age.[1] MM is also more common in women, more so than SM (Table 1).[9,10,40,41] Interestingly, Tsermoulas et al (2018) reported a female to male ratio for sporadic MM as 3.9:1, compared to 1.9:1 for radiation-induced MM.[8] The counterintuitive finding that RIM also has a female preponderance concurs with previous studies.[21] In contrast, the SEER study found the female to male ratios of SM and MM were 2.9:1 and 2.3:1, respectively.[11] The highest female predilection was reported by Ramos-Fresnedo et al (2021), with a female to male ratio of 3.2:1 for the whole cohort; but 2.9:1 for SM and 8.6:1 for MM (Table 1).[38]

Etiology, Presentation, and Imaging

Information about etiology, presentation, and imaging findings in the literature suffers from variable definitions and quality of data. Tsermoulas et al (2018) report most extensively, with 79.7% of MM patients with sporadic disease at presentation, 19.5% with RIM and 0.75% with familial syndromes. The majority (88%) were synchronous tumors, and the remaining were metachronous. Overall, 50.4% of patients were symptomatic, and of these, 10% presented with seizures. The remaining 49.6% had incidental and asymptomatic tumors. A total of 39% of tumors were located at the convexity, 35% at the midline, and 25% at the skull base, and 67% were small (maximum diameter ≤2 cm), 22% medium (>2 and ≤4 cm), and 11% large (>4 cm). At presentation, 90% of patients with large meningiomas were symptomatic. The proportion of symptomatic patients with medium and small meningiomas was 43% and 16%, respectively.[8] Pereira et al (2019), in their systematic review, only provide information on tumor location. The vast majority of the tumors were located at the convexity (65.3%–74.5%), followed by the skull base (22.0%–25.1%), and ventricular (45%–0.4%).[10]

Genetics of Multiple Meningiomas

The genetic features of sporadic meningiomas have been reviewed extensively elsewhere and include frequent initiating mutations, deletions, or epigenetic silencing of *NF2* and *4.1B* (Table 2).[18,43] It is difficult to delineate meningioma initiating genes from those purported to increase the aggressiveness of tumor growth, so-called "progressor" genes, though numerous genomic alterations common among higher grade meningiomas signal the possible loci of such progressor genes. Losses on 1p, 10q, 14q, 6q, and 18q, and gains on 1q, 9q, 12q, 15q, 17q, and 20q are associated with higher grade meningiomas with multiple genes implicated at each locus (Table 2).[18]

Multiple meningiomas may be both sporadic and familial, with these groups likely representing unique disease processes. Familial MM can be attributed to numerous inherited cancer syndromes, with germline mutations in genes thought to be related to meningioma initiation and progression (shown in parentheses), including NF2 (*NF2*), Cowden syndrome (*PTEN*), Gorlin syndrome (*PTCH1*, *SUFU*), Werner Syndrome (*LMNA*), Li Fraumeni syndrome (*TP53/CHEK2*), von Hippel Lindau syndrome (*VHL*), and Multiple Endocrine Neoplasia type I (*MEN1*).[18] In contrast, present evidence suggests sporadic MM arises from new somatic mutations, although germline mosaicism is difficult to exclude.[24,30–32,44,45] Early studies into MM identified karyotypic differences between tumors, suggesting independent tumorigenesis at disparate sites, albeit further investigation has demonstrated MM with identical *NF2* mutations alongside X-inactivation of the same chromosome in non-syndromic patients, suggesting common clonal origin with presumed subarachnoid spread, or inherent genetic instability in certain patients.[24,30–32,44,45] Of interest, *NF2* mutations play a role in sporadic MM, but not necessarily in familial MM in non-NF2 affected families, suggesting unique disease pathways in these 2 entities.[42,46] Contributing genes in familial MM, not otherwise explained by hereditary syndromes, are not well understood, although some candidate genes have been examined.

Several unique genes have been observed to contribute to familial non-NF2 related MM, including *SMARCB1*, *SMARCE1*, *SUFU*, and *PCD10*/*CCM3* (Table 2).[47–52] *SMARCB1* is located at 22q11.2, with functional relevance in inhibiting G_0–G_1 transition via the p16-Rb pathway, and regulating the canonical Wnt and hedgehog signaling pathway, functioning as a tumor-suppressor.[18,53] *SMARCB1* mutations with loss of heterozygosity have been noted in familial MM, with some reports suggesting concurrent inactivation of *NF2* and *SMARCB1* contributes to meningioma development through a 4-hit hypothesis; in contrast, in 1 study of 45 patients with sporadic MM, germline *SMARCB1* mutations were not detected in any patient, suggesting *SMARCB1* mutations may overall contribute rarely to meningioma development.[47,48] *SMARCE1* produces BAF57, which mediates chromatin structure, with *SMARCE1* also regulating apoptosis through CYLD expression; *SMARCE1* mutations with loss of protein expression in tumor cells have been noted in 4 families with multiple spinal meningiomas without *NF2* or *SMARCB1* mutations, suggesting this gene may also play a role in familial MM.[49] Similar to *SMARCB1*, *SUFU* has an antiproliferative function by producing a gene product that binds to the hedgehog-pathway mediator GLI1, reducing nuclear translocation and transcription factor function; SUFU missense mutations resulting in altered protein structure and function have been detected in 5 siblings with MM, in the absence of germline and tumor *NF2* gene mutations.[52] Finally, *PCD10/CCM3* inactivation is thought to contribute to MM and multiple cerebral cavernous malformations as the *PCD10/CCM3* gene product is pro-apoptotic, albeit given a lack of further assessment of the contribution of other mutations typically associated with meningiomas in these cases is not clear.[50,51]

Table 2. Role of genetic alterations in multiple meningiomas

Chromosome	Gene	Product	Sporadic	Non-NF2 Familial	RIMs	Comments
1			◦ (1p gain)			
	EPB41		◦		◦	1p loss candidate genes; second most common chromosomal abnormality
	GADD45A		◦		◦	
	TP73		◦		◦	
	CDKN2C	$p18^{INK4c}$	◦		◦	
	RAD54L		◦		◦	
	ALPL		◦		◦	
	ARID1A				◦	
3	*PCD10/ CCM3*			◦		
6			◦ (6q loss)			
7	*SMO*				◦	
9			◦ (9q gain)		◦ (9q loss)	
	CDKN2A ARF CDKN2B	$p16^{INK4a}$ $p14^{ARF}$ $p15^{INK4b}$	◦			9p loss candidate genes
			◦			
			◦			
10					◦ (10p loss)	
	DMBT1		◦			10q loss candidate genes
	MXII		◦			
	PTEN		◦		◦	
	SUFU	SUFU		◦		
11	*HRAS*				◦	
12			◦ (12q gain)			
	KRAS				◦	
14	*NDRG2*		◦			14q loss candidate genes; third most common chromosomal abnormality
	MEG3		◦			
	SMARCE1	BAF57		◦		
	AKT1				◦	
15			◦ (15q gain)			
16	*TRAF7*				◦	
17	*RPS6KB1*		◦			17q gain candidate gene
	TP53		◦			
18					◦ (18q loss)	
	4.1B	DAL-1	◦			Up to 60% of sporadic meningiomas noted losses
	MADH2		◦			18q loss candidate gene

Table 2. Continued

Chromosome	Gene	Product	Sporadic	Non-NF2 Familial	RIMs	Comments
	MADH4		∘			
	DCC		∘			
	APM-1		∘			
19					∘ (19q loss)	
20			∘ (20q gain)			
22	*BAM22*		∘		∘	22q loss candidate genes; commonest genetic abnormality in meningioma
	MN2		∘		∘	
	LARGE		∘		∘	
	IN1		∘		∘	
	NF2	Merlin	∘		∘	
	SMARCB1			∘		

This table collates the role of reported genetic alterations in high grade, non-NF2 related familial, and radiation-induced meningiomas (RIMs). Columns list in order chromosomes, relevant genes, and gene products, with "∘" signifying the relevant gene contributes to the various meningioma types. Where "∘" is listed without a specific genetic abnormality, chromosomal alterations without identified candidate genes are listed in parentheses. Represents a sysnthesis of Riemenschneider et al, Umansky et al, Bachir et al, Casalone et al, Zhu et al, Stangl et al, Larson et al, Shen et al, Suppiah et al, Lomas et al, Torres-Martin et al, Heinrich et al, Christiaans et al, Hadfield et al, Smith et al, Garaci et al, Riant et al, Aavikko et al, Kohashi et al, Shoshan et al, Barboza et al, Agnihotri et al, Kimura et al, Petrilli et al.[18,20,22,24,30,32,42–53,66,69–72]

Radiotherapy is a major modality for the treatment of intracranial and extracranial tumors. Meningiomas are the most common form of radiation-induced neoplasm, are frequently multiple,[21,54] and the first patient with a RIM was reported in 1953.[55] It has been reported that patients who received 1–2 Gy of radiation in childhood have a 9.5-fold increased risk of developing a meningioma,[56,57] and the cumulative risks of radiation-induced brain tumors after radiotherapy are 2.0% at 5 years and 8.9% at 10 years.[58] To define a meningioma as radiation-induced, it must fulfill the following criteria: (i) the tumor must arise in the irradiated field; (ii) the histological features must differ from those of any previous neoplasm in the region; (iii) the tumor must occur after an interval sufficient to demonstrate that the neoplasm did not exist prior to irradiation (usually years); (iv) this type of tumor must occur frequently enough after irradiation to suggest a causal relationship; (v) this type of tumor must have a significantly higher incidence in irradiated patients than in an adequate control group; (vi) there must be no family history of a phacomatosis; and (vii) the tumor must not be recurrent or metastatic.[19,21,54,59] RIM are often divided into 3 groups based on the radiation exposure: (i) low dose (<10 Gy); (ii) moderate dose (10–20 Gy); (iii) high dose (>20 Gy),[19] other authors define all doses >10 Gy as high dose.[20,21,60] RIM are characterized by lower patient age at diagnosis, an increased rate of multiplicity (Figure 1), and higher risks of recurrence after treatment and atypical or anaplastic histology, when compared to nonradiation-induced SM.[20,21,54] Furthermore, Gillespie et al (2021) reported that RIM demonstrates high absolute and relative growth rates, indicating an increased risk for clinical and radiological progression.[61]

life.[19,59,62] RIM occur typically in a younger population,[21,63] with the mean age at presentation for patients treated previously with high dose radiation ranging from 29 to 35 years and for those with low dose radiation from 45 to 58 years.[20,21,54] The latencies for RIM arising after low dose radiation range from 12 to 46 years, although most studies report between 30 and 40 years. RIM caused by high dose radiation has a very broad reported latency range, from only 14 months up to 63 years, with a tendency for shorter latency in patients treated with higher doses and at a younger age.[21,54,64,65] Nonetheless, in the majority of series of RIM related to high dose radiation, the reported latencies are between 12 and 25 years.[21,54,66]

The incidence of WHO grades 2 and 3 meningiomas are higher in patients with RIM than in those with SM.[62,67] Musa et al (1995) reported that for RIM after high dose radiation, 76% were benign, 19% atypical, and 4% malignant and for RIM after low dose radiation, 90% were benign and 10% atypical.[60] Godlewski et al (2012) reported 88% of RIM after high dose radiation were WHO grade 1 and 12% WHO grade 2.[21] Yamanaka et al in their 2017 study had WHO grade available in only 205 of 251 RIM, and 68% were WHO grade 1, 27% WHO grade 2, and 5% WHO grade 3.[63] RIM have a reported recurrence rate between 18.3% and 25.6%, compared with approximately 3%–11.4% for spontaneous meningiomas in these studies.[20,21,54,62,63,67,68]

The incidence of multiple RIM is reported to range from 4.6% to 29%.[20,54] Sadetzki et al (2002) reported 15.8% of RIM to be multiple in 253 patients.[62] Yamanaka et al (2017) reported 11.9% in a systematic review of 251 patients with RIM in which they also noted that MM and atypical/anaplastic meningiomas were more common in the

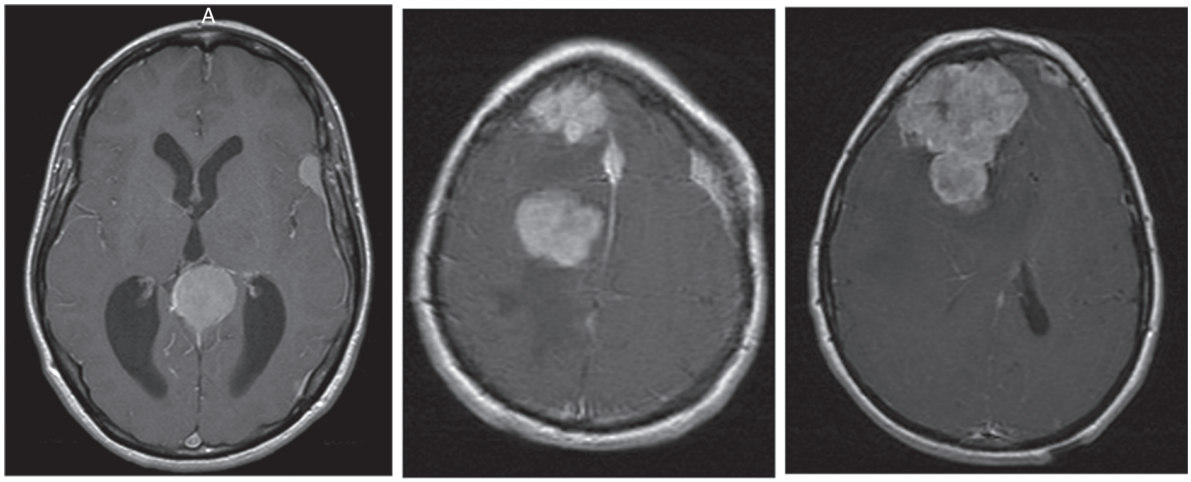

Figure 1. (Left) MRI of sporadic multiple meningiomas; 1 large symptomatic tumor requiring treatment and 1 small tumor to be observed. (Right) MRI scans of radiation-induced multiple meningiomas.

intermediate dose and high dose RIM than in the low dose RIM.[63] Godlewski et al (2012) reported a higher incidence of multiple RIM of 38.5% in a series of 26 patients with RIM after high dose radiation.[21]

Genetics of Radiation-Induced Meningiomas

Meningiomas are the most common ionizing radiation-induced neoplasm, but the etiology is unclear, although relative susceptibility of arachnoid cap cells to radiation has been suggested.[20,69] Ionizing radiation induces hydroxyl free radical generation, causing DNA damage, with faulty DNA repair resulting in point mutations, translocations, and gene fusions, alongside direct ionizing radiation-induced DNA damage.[20,70] Although higher doses of radiation of 22–87 Gy have been associated with RIM with latencies of 19.5 years, even lower doses of 1–2 Gy, such as used to treat tinea capitis and for dental X-rays can be associated with a 9.5-fold increased risk of RIM with latencies of 12–49 years.[20] The genetic development of RIM is not understood, although current evidence suggests they develop through mechanisms distinct from sporadic meningiomas. *NF2* mutations are much less common, with only 0%–24% of RIM harboring *NF2* mutations.[70] Loss of 22q is noted in RIM as well, albeit at a lower rate than sporadic meningiomas.[69] Similarly, mutations in other genes typically associated with meningiomas, including *AKT1, SMO, TRAF7, ARID1A, HRAS, KRAS,* and *NRAS* are uncommon in RIM.[70] In contrast, mutations in *p53* and *PTEN* and losses of 1p, 9q, 19q, 18q, and 10p have been reported in RIM (Table 2).[69,70] Very little has been reported on genetic characterization of synchronous RIM, although 1 report of 2 patients bearing synchronous RIM demonstrated distinct mutational profiles suggesting a distinct origin for each tumor, rather than the subarachnoid seeding that has been suggested for sporadic MM.[70] Ultimately, the definitive pathophysiology of RIM in unknown, though current evidence suggests a distinct pathogenetic mechanism, unique from sporadic meningiomas, most strongly evidenced by the lower rate of *NF2* mutation and with multiple synchronous RIM potentially arising distinctly, rather than through subarachnoid spread.[69,70]

Neurofibromatosis Type 2 and Multiple Meningiomas

NF2 is a rare autosomal dominant familial disorder associated with MM,[42] and due to germline loss of the *NF2* tumor-suppressor gene. NF2 increases the risk of meningiomas, with approximately 50% of NF2 patients bearing MM.[18] The management of patients with NF2 is complex and out of scope. However, one of the most important differences in the management of sporadic and familial MM is the need for genetic counseling, which is relevant in NF2.

Somatic chromosome 22q and *NF2* loss is a common finding in sporadic meningiomas, although the relationship between germline *NF2* loss in neurofibromatosis and the generation of meningiomas is more complicated.[18] *NF2* encodes merlin, a cytoskeletal tumor-suppressor protein which mediates cell growth arrest through downstream effects on mTORC1 and PAK, as well as affecting cell growth and contact inhibition.[18] Merlin is also thought to play a role in cytoskeletal function, including mitotic spindle formation, and loss of merlin is thought to increase the risk of chromosomal instability.[18] The implication of this instability is not clear, though chromosome 22 loss and haploinsufficiency are the commonest genetic aberration among meningiomas.[18] This suggests that loss of the remaining NF2 allele is the most significant factor in the generation of MM. However, numerous mechanisms of *NF2* loss are observed among sporadic meningiomas, including epigenetic silencing, as well as inactivation of merlin through calpain-mediated proteolysis.[44,71,72] Additionally, other chromosomal and genetic abnormalities are known to be associated with higher grade

meningiomas, including *TERT* mutations which in sporadic meningiomas cooccur with *NF2* losses in 80% of cases.[22] Further investigation of other genetic events precipitating MM in NF2 is needed.

Treatment, Follow Up, and Prognosis

The therapeutic modalities available for MM include surgery, stereotactic radiosurgery, and fractionated external beam radiotherapy. However, many tumors do not require treatment, with studies reporting between 32% and 44% of tumors and 64% of patients requiring active treatment.[8,10] Tsermoulas et al (2018) most comprehensively outline the treatment of MM patients and reported that 1 in 4 required treatment of more than 1 tumor. Their mean follow-up was 7 years (range 1–17 years), and 13% of treated patients required salvage treatment for recurrence. Overall, 41% of their patients were treated at presentation, 38% because they had symptoms, and 3% because they were expected to imminently become symptomatic. Of the remaining patients, 39% required later treatment because they developed symptoms or because of tumor growth. Time from presentation to treatment for this group was on average 4.4 years (range from 7 months to 12 years). Of the patients treated at presentation, 33% required treatment of a different meningioma on an average of 5 years (range from 9 months to 18 years) after diagnosis. Treatment strategies included surveillance for 36% of patients, resection of at least 1 tumor for 50%, and radiation therapy for 14%. Of the surgically treated patients, 13% had more than 1 meningioma removed during the same operation, 38% had surgery at presentation, and 12% during surveillance. In total, 19% of tumors were surgically treated. Among patients treated with radiotherapy, multiple lesions were treated in the same session for 50%. Of patients treated with surgery, 16% had repeat treatment for recurrent disease, but 84% had good control for an average 8.5 years of follow-up (range 0.5–23 years). Of the surgically treated patients, 13% underwent radiotherapy (mainly Gamma Knife Radiosurgery) for a different meningioma. As first-line treatment, 20% of patients underwent radiotherapy for 12% of meningiomas, 37% of these were treated at presentation, and the rest during surveillance, and 67% of patients had radiation therapy only, and the remaining had both radiation therapy and surgery for different meningiomas. Radiation therapy was Gamma Knife Radiosurgery in 70%, fractionated radiation therapy in 22%, and a combination of both in 7%.[8] Other studies have reported a tumor

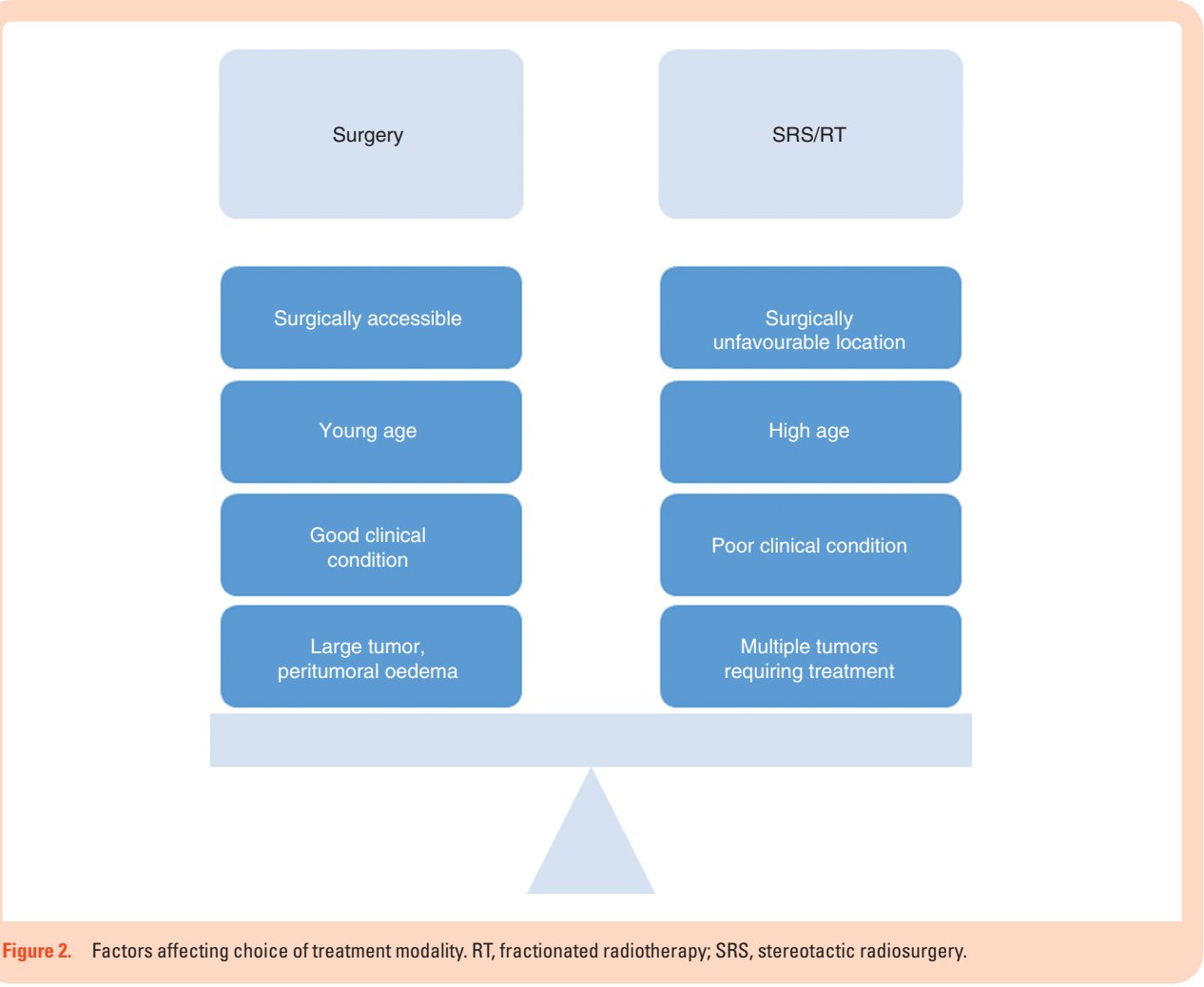

Figure 2. Factors affecting choice of treatment modality. RT, fractionated radiotherapy; SRS, stereotactic radiosurgery.

recurrence rate of 8% after follow-up care for an average of 21.4 ± 8.6 years.[10]

Treatment Recommendations

The therapeutic strategies for patients with MM must be customized because of the nature of the tumors and the potential consequences of treatment for different patients vary considerably.[73] In patients with MM, the overall goal is tumor control, as surgical removal of all tumors is seldom possible, and it is necessary to have the perspective of chronic disease. The multiplicity brings particular challenges, including localizing the symptomatic lesion or lesions, choosing the most suitable treatment modality, avoiding treatment risks, and predicting the behavior of individual untreated tumors. It is crucial to consider that a patient with MM might need repeated treatments over their lifetime (Figure 1).

An important consideration is the likely growth rate of any tumor. The natural history and growth rate of MM were investigated by Wong et al 2013. They analyzed 55 tumors in 12 patients with an average follow-up of 61 months (range 24–101 months).[7] They reported an average growth rate of 0.46 cm^3/year (range 0.57–2.94 cm^3/year), which is similar to that reported for incidental found SM.[7,74] The relationship between tumor multiplicity and growth rates was also analyzed, but no correlation between the number of meningiomas per patient and growth rate was observed.[7]

Although meningiomas are common, the levels of evidence for their treatment are surprisingly low.[6,73,75] Management might appear to be standardized, but controlled clinical trials are uncommon, so standards of care are to a great extent defined by local experience, long-standing tradition, and occasionally experience-based practice. Furthermore, in many cases, more than 1 treatment option is reasonable. In 2016, the European Association of Neuro-Oncology (EANO) issued its first guideline on the diagnosis and treatment of meningiomas.[73] Since then, the level of evidence for diagnostic and clinical decisions has increased, including data from controlled clinical trials and the new fifth Edition of the WHO Classification of Central Nervous System Tumors. Therefore, EANO has updated its meningioma treatment guideline in 2021.[75] Specific recommendations regarding MM are not discussed in these guidelines but are warranted. To the best of our knowledge, this is the first attempt to present management guidelines for MM (Figures 2 and 3).

Observation

The increasing number of incidental, asymptomatic meningiomas diagnosed through neuroimaging demands the development of tailored treatment and follow-up strategies.[6] Most of these meningiomas are WHO grade 1, and as treatment-related morbidity is not negligible, it is difficult to recommend treatment at this stage.[6] In the majority of patients, clinical or radiological progression occurs within 5 years of diagnosis, and Islim et al (2019) argue that regular monitoring after this time may be less frequently required.[76]

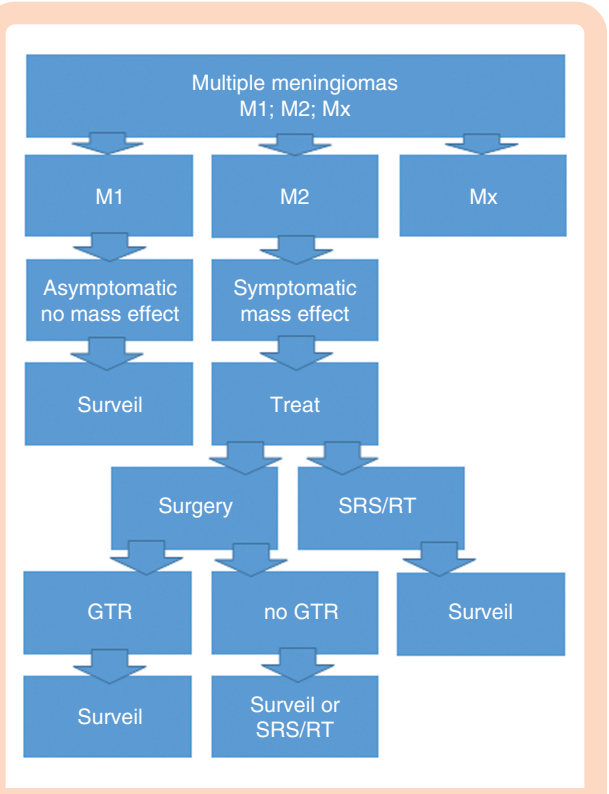

Figure 3. Management recommendations for multiple meningiomas. Surveillance: annual MRI scans for 5 years, thereafter interval can be doubled. GTR, gross total resection; RT, fractionated radiotherapy; SRS, stereotactic radiosurgery.

Based on these findings, a prognostic model to guide personalized monitoring of incidental meningioma patients has been developed, which includes both SM and MM.[76] The model combines data on patient age, performance status, comorbidities, and MRI features to categorize patients as low, medium, or high risk for growth and progression, allowing an individualized monitoring strategy to be developed. Factors such as tumor hyperintensity, increasing volume, proximity to critical neurovascular structures, and peritumoral signal change all increase the risk of disease progression within the first 5 years following diagnosis. Patients can then be followed clinically and radiologically with different schedules corresponding to predicted rates of disease progression. Furthermore, the study showed that the majority of incidental meningiomas remain stable during follow-up and growth plateaus after 5 years. Finally, the model showed little benefit to rigorous monitoring in low-risk and older patients with comorbidities, as they are very unlikely to require intervention during their estimated lifetimes, and continued imaging surveillance was not recommended.[76]

So, an increasing body of evidence indicates that a large proportion of patients with both SM and MM do not require active treatment. For the vast majority of patients, this results in regular surveillance, including repeated MRI scans.[8,10,75–77] The evidence for this strategy for MM is not as strong as for SM, but is enough to suggest that asymptomatic patients with MM can be safely managed with

serial imaging until persistent radiological or symptomatic growth. In consensus with EANO, annual MRI scans are recommended in suspected or WHO grade 1 meningiomas for 5 years. Thereafter, intervals can be doubled.[75] Based on the results presented by Islim et al (2020), it seems reasonable to individualize follow-up, especially in comorbid elderly patients.[76]

Surgery

Surgery is the primary treatment modality for the majority of symptomatic or growing meningiomas in patients with both SM and MM, aiming to relieve mass effect and neurological symptoms, as well as obtain a tissue diagnosis. Despite the lack of randomized trials comparing surgery to other therapies, this is a well-established approach. The evidence for surgery as first-line treatment stems from many case series showing that the extent of resection (EOR) is an important prognostic factor.[75,78,79] The primary goal of meningioma surgery is maximum safe resection, with low morbidity and preservation of neurological and cognitive function. If possible, the aim is gross total resection (GTR), but the EOR is additionally determined by a number of factors, including tumor location, consistency, and size, as well as proximity to or involvement of critical neurovascular structures.[75] The principles are the same in patients with MM, but surgical decisions are more challenging as resection of more than 1 tumor may be necessary although removal of all tumors is seldom a reasonable goal. Tumors may be left after successful surgery, as the procedure should be focused on the symptomatic or growing tumors. Thus, patients with MM are rarely "cured" with surgery in the same sense that those with SM may be. When GTR is not a realistic goal, the aim should be a safe subtotal resection with preservation of neurological and cognitive function. The management of residual tumors should be individualized, with options including monitoring, postoperative conformal fractionated radiotherapy or stereotactic radiosurgery (SRS).[75]

Before the surgery, it is vital to discuss with the patient the surgical goals, as well as the surgical risks. In patients with MM, it is important to clearly explain the goals of treatment, particularly where not all tumors can be removed and disease control is the aim. The patient should be prepared for multiple treatments and lifelong surveillance.

Radiosurgery

Stereotactic radiosurgery is an important alternative to surgery for small tumors, tumors in locations carrying high surgical morbidity and those in elderly or unwell patients.[75] Bir et al (2017) showed that local control with SRS of small intracranial meningiomas with a diameter of 3 cm or less was comparable to Simpson Grade 1 resection.[80] They also showed that recurrence-free survival was longer in the SRS group compared to patients with incomplete resection. Thus, subtotal resection may not be indicated for small meningiomas.[80] However, improvement of symptoms was more likely after surgery.[80] Additionally, 2 retrospective studies showed a reduction of tumor size after SRS or hypo-fractionated radiotherapy predicted long-term tumor control after 5 and 10 years.[81,82] In these series, the 10-year recurrence-free survival was 93.4% and 95.7%, respectively.[81,82] As simultaneous treatment of spatially separated tumors with good long-term results is possible,[83] SRS plays an even more important role for patients with MM.[8] In particular, for skull base meningiomas with cranial nerve and vascular involvement, GTR is seldom feasible and a multimodal approach using subtotal resection and SRS is increasingly used.[75,84] Thus, the role of combined treatment modalities will increase for meningiomas, in particular for patients with MM. Important complications to consider after SRS include peritumoral edema and radiation-induced neuropathy, and endocrinopathy.[80,81,84,85]

Fractionated External Beam Radiotherapy

Fractionated external beam radiotherapy continues to contribute to the management of meningiomas. It is a well-established modality for patients with meningiomas that cannot be safely resected, or after incomplete resection. Multiple trials suggest the benefits of fractionated radiotherapy for patients with WHO grades 2 and 3 meningiomas with acceptable toxicity. In a retrospective cohort study of WHO grades 2 and 3 meningiomas who underwent surgical resection and/or radiotherapy, the 5-year overall survival (OS) was 75.9% for patients with WHO grade 2 tumors and 55.4% for patients with WHO grade 3 meningiomas. Furthermore, in patients WHO grade 2 meningiomas, gross total resection and postsurgical radiotherapy were independent predictors of improved survival.[75]

In the first clinical outcomes report of the prospective NRG Oncology RTOG 0539 trial results for the intermediate-risk group (patients with recurrent WHO grade 1 with any EOR, or newly diagnosed WHO grade 2 after GTR with fractionated radiotherapy) were presented; among these 48 patients, 3-year progression-free survival (PFS) was 93.8%, with 3-year OS 96% and local failure 4.1%.[75] No significant difference in outcome was observed between patients with recurrent WHO grade 1 and WHO grade 2 meningiomas receiving gross total resection.[75] In the second report from the trial, the results from the high-risk group (new or recurrent WHO grade 3 tumors with any EOR, recurrent WHO grade 2 tumors with any EOR, and recurrent WHO grade 2 tumors after subtotal resection with prior fractionated radiotherapy) were presented; of these 53 patients with a median follow-up of 4.0 years, 3-year PFS was 58.8%, 3-year local control was 68.9%, and OS was 78.6%. The authors concluded that the results support the use of postoperative radiotherapy for these patient groups.[75]

Patients with meningiomas previously treated with radiation are a challenging cohort, due to the low reirradiation tolerance of tissues in the previously exposed field. Available data is very limited, but some papers suggest that reirradiation can be indicated in selected cases for the treatment of recurrent meningiomas, depending on the previous dose distribution, time between primary and reirradiation, and location, especially in the vicinity of organs at risk.[86]

It is clear that fractionated radiotherapy can avoid additional surgical procedures but with the risk of long-term

toxicity, including neurocognitive impairment, hypopituitarism, and radiation-induced tumors.[75] However, technological advances over the past decades in imaging, target delineation, and 3-dimensional planning have improved tumor coverage and critical structure avoidance that have rendered radiation more accurate, efficacious, and safe.

Pharmacotherapy

There are currently no effective pharmacological treatments for meningioma, and a discussion of the treatment horizon is beyond the scope of this review.[43,87] When available, patients with MM will particularly benefit, due to the possibility of treating all their tumors at once,. It is difficult to make recommendations or predictions in the absence of positive clinical trials and further research is needed.

Cognitive Function

Multiple studies have shown cognitive impairment in meningioma patients both pre and postoperatively.[88,89] The domains of memory, attention, and executive function are most often affected. Preoperative impairment may be due to anatomical location, psychosocial factors, epilepsy, and its treatment or raised intracranial pressure caused by the tumor or tumor-related edema. Complexity increases in patients with MM as it may not be clear which tumor or tumors are responsible for the cognitive dysfunction. Even if no causality has been shown, there is a correlation between cognitive impairment and frontal or temporal tumor location, tumor size, and edema volume.[73,88,90,91] Cognitive function normally improves after surgery.[88,92,93] Seizures and antiepileptic drugs may explain cognitive impairment postoperatively.[94] Surprisingly, it has been difficult to show any clear correlation between tumor lateralization and cognitive function postoperatively.[88] Long-term postoperative cognitive impairment is seen in meningioma patients with significant preoperative cerebral brain edema.[88,91] Interestingly, no correlations between radiotherapy and cognitive function have been found even after long follow up.[94,95] In patient with MM, the effects of multiple treatments, residual tumors, treatment of epilepsy and psychosocial stressors are likely to be relevant and potentially cumulative.

Quality of Life

In recent years, reduction in HRQoL has been increasingly recognized in meningioma patients.[96,97] HRQoL is impaired preoperatively in meningioma patients, and even if neurological deficits improve after surgery, long-term reduction of HRQoL can occur[96,98,99] in cognitive, emotional and social domains and be complicated by sleep disturbance, pain, anxiety, and fatigue.[96,97] Furthermore, the number of patients able to drive or return to work decreases over time with a significant socioeconomic burden.[96,100] Poor HRQoL has variously been reported to be associated with large tumor size, high WHO grade, tumor recurrence, shorter time since diagnosis, age of ≥50 years, posttraumatic stress, personality change, confusion, left hemisphere tumor location, headache, and seizures.[97,99,100] Self-evidently in patients with MM, as for cognitive dysfunction, the effects of multiple tumors and their treatment may result in more profound effects on HRQoL compared to patients with SM, but studies are lacking.

Prognosis

To the best of our knowledge, the 2020 SEER study is the first survival analysis of a large cohort of patients with MM and showed that the number of lesions, age at diagnosis, and sex influence OS in MM patients.[11] The median survival was 180 months for patients with SM and 94 months for patients with MM. The analysis showed a progressive decrease in OS for every additional lesion. Patients treated with radiation had a longer OS compared to patients who didn't receive radiation. Female patients had a longer OS. Analysis of the male cohort showed that MM reduced OS starting at age 41, with shorter OS for every added decade. A similar analysis of the female cohort showed that MM reduced OS starting at age 51, with shorter OS for every added decade. As these results represent a single study, the applicability is limited and should be applied with caution.[11]

A recently-published study by Ramos-Fresnedo et al (2021) investigated the impact of a number of meningiomas and clinical characteristics on PFS in patients with WHO grade 1 meningiomas, excluding those with WHO grades 2 or 3 meningiomas, NF2, a schwannoma or intracranial malignant tumor.[38] The cohort consisted of 838 adult patients; 742 (88.54%) had a SM, and 96 (11.46%) had MM. They showed a shorter PFS and time to second intervention (TTSI) for every additional meningioma, as well as a shorter PFS and TTSI for patients with MM compared to patients with a SM. They also showed that African Americans had a shorter PFS, but young age and adjuvant therapy with radiation were associated with longer PFS.[38]

Conclusion

Published data on MM is rare and mostly limited to case reports and small case series. Nevertheless, we have reviewed the MM literature and created the most extensive and comprehensive review on the subject, including an evidence-based management paradigm, which will serve as a strong baseline for clinical decision making, as well as for future studies. The presented epidemiological data indicate that the true MM incidence is much higher than previously thought, which illustrates that further research and more developed treatment recommendations are needed. Even if there are some clear similarities between SM and MM, such as age and sex distribution, tumor grade, and growth rate, there are also distinct differences such as the likelihood of underlying genetic diseases, treatment goals, and prognosis. The management of patients with MM is complex, including multiple treatments, sometimes with different modalities, and lifelong surveillance. We advocate that MM should be regarded and managed as a chronic disease.

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genetics | multiple meningiomas | management | surgery.

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