

## Mental health disorders in patients with untreated meningiomas: an observational cohort study using the nationwide MarketScan database

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### Abstract

**Background.** Meningiomas are the most common primary tumor of the CNS. Studies investigating the impact of a brain tumor diagnosis on mental health disorders (MHDs) in patients have been limited. The objective of this work is to characterize the incidence and factors affecting the presence of MHDs in untreated meningiomas.

**Methods.** Using a large-scale private payer database, MarketScan, we performed a retrospective study of patients with an untreated meningioma and corresponding MHD.

**Results.** We found that in patients diagnosed with an untreated meningioma, approximately 16% were diagnosed with an MHD within 1 year of the diagnosis of the meningioma.

**Conclusion.** By identifying risk factors, appropriate screening can focus on patients at high-risk for the development of MHD.

### Keywords

CNS | meningioma | mental health disorders | MHD

Meningiomas are the most common primary tumor of the CNS, with an estimated incidence of 7.86 per 100 000 population per year.<sup>1,2</sup> When symptomatic, the primary presenting complaints include headaches, seizures, or focal neurologic deficits; however, as many as three-quarters of meningiomas are discovered incidentally and are asymptomatic.<sup>3–6</sup> The vast majority of these lesions are histologically benign, and therefore many asymptomatic meningiomas are left untreated, meaning that they are not surgically resected or treated with radiosurgery, but are instead monitored through serial imaging and do not require further intervention. With the dramatic increase of advanced cranial imaging in the United States in recent decades, there has been a 3-fold increase in the discovery of asymptomatic meningiomas and a proportionate increase in patients with untreated meningiomas.<sup>7</sup>

Studies investigating the impact of a brain tumor diagnosis on mental health disorders (MHDs) in patients have been limited. Existing studies have primarily examined patients with malignant gliomas and have consistently shown a significant psychological cost. Fifteen percent of glioma patients will meet diagnostic criteria for depression, with an equal number suffering from subclinical depressive symptoms.<sup>8</sup> Similarly, rates of anxiety in brain tumor patients range between 30% and 63%.<sup>9–11</sup> These psychiatric comorbidities are associated with decreased functional status, impaired quality of life, poor cognitive status, and reduced overall survival.<sup>12–16</sup>

In contrast to malignant gliomas, the impact of untreated meningiomas on MHDs is neither described nor discussed in the literature. Here, we characterize the incidence and factors

affecting the presence of MHDs in untreated meningiomas in a large-scale private payer database.

## Methods

### Study Design

This retrospective observational cohort study used administrative claims data collected from the IBM Health MarketScan Research Database to characterize MHDs in patients with untreated meningiomas. This commercial database contains the inpatient and outpatient administrative medical data of approximately 225 million privately insured patients since 1995<sup>17</sup>. Because we used a deidentified, external (outside our institution) database for this study, no institutional review board approval or patient consent was needed. The database provides detailed cost, use, and outcomes data for health-care services performed both in inpatient and outpatient settings across a variety of health plans. This includes preferred provider organizations, point of service plans, indemnity plans, and health maintenance organizations. The medical claims are linked to outpatient claims and person-level enrollment data using unique enrollee identifiers.

### Patient Selection

Eligible patients for the cohort were identified from the database by querying International Classification of Diseases, Ninth Revision (ICD-9) codes corresponding to meningioma (192.1, 2252, 2376). Eligible patients had continuous enrollment in the database for 1 year prior and 1 year following the diagnosis. Treatment status was determined through presence of corresponding Current Procedural Terminology (CPT) codes. Given the limitations of the database, presenting symptoms were inferred from a query of ICD-9 codes

diagnosed in the 6 months prior to diagnosis of the meningioma but that had not been present prior (Table 1).

For assessment of MHDs, we used ICD-9 codes corresponding to episodic mood disorders, including depression (296.0-296.9), anxiety (300.0-300.9), nonalcohol drug dependence (304.0-304.9), adjustment reaction (309.0-309.1), and depressive disorder not otherwise specified (311.0-311.9). To capture those without an official MHD diagnosis, dispensing records were used for the psychotropic medications listed in the Supplement. This combined cohort represented the primary analysis. A subgroup analysis was performed for those patients who developed only depression and only anxiety. History of tobacco use was obtained from using a combination of ICD-9 Clinical Modification (ICD-9-CM) codes and CPT codes related to smoking behavior and history of alcohol use from the ICD-9-CM codes for alcohol dependence. This methodology is consistent with our previously published work.<sup>18</sup> For a subgroup analysis, we looked at those with ICD-9 codes for depression and for anxiety separately.

### Statistical Analysis

All statistical analysis was conducted in SAS version 9.4 software (SAS Institute). Univariate analysis was conducted to assess statistical significance of differences in proportions using a chi-square test for categorical variables. In the multivariable logistic regression model, we adjusted for residence (rural or urban), age, sex, region (East, South, Midwest, Northwest or Unknown), history of smoking, history of alcohol dependence, headache, seizures, visual symptoms, vertigo, hemiplegia, nonspecific neurologic symptoms (each, yes/no), and Charlson Comorbidity Index. Descriptive results are presented as proportions and the multivariable regression results are presented as adjusted odds ratio (aOR) with 95% CI. The

**Table 1.** International Classification of Diseases, Ninth Revision, and Current Procedural Terminology (CPT) Codes

Cohort	Code
Benign neoplasm of cerebral meninges	225.2
Malignant neoplasm of cerebral meninges	192.1
Neoplasm of meninges of uncertain behavior	237.6
Treatment (CPT codes)	
Supratentorial meningioma resection	61512, 61519
Infratentorial meningioma resection	61519
Presentation (identified in the 6 mo prior to diagnosis, but not prior to that)	
Headache	339, 346
Seizure	345, 780.3
Visual symptoms (papilledema, field cut, visual disturbance)	368, 369, 377.00
Hemiplegia/Hemiparesis	342
Hearing loss	389
Dizziness/Vertigo	780.4, 386.1, 386.2, 386.9
Nonspecific neurologic symptoms (gait, smell, taste, coordination, aphasia, dysarthria, alterations in consciousness etc)	780.0, 780.97, 780.2, 781.0, 781.1, 781.2, 781.3, 781.4, 784.3, 784.5

statistical tests were significant if the *P* value was less than .05 (2-sided). Similar univariate and multivariable analyses were performed for the depression and anxiety subgroups.

## Results

A total of 18 415 patients with newly diagnosed meningioma were identified from the database. Of these, 15 320 patients did not undergo treatment within 1 year of diagnosis and were selected for further analysis. The demographic details for this cohort are detailed in Table 2. Of these patients, approximately one-third carried a diagnosis of an MHD at the time of their meningioma diagnosis (*n* = 5132).

Of the patients without an MHD diagnosis at the time they were diagnosed with a meningioma, 1639 (16.09%) went on to develop an MHD in the year following diagnosis of their meningioma. Of the 1639 patients with newly diagnosed MHDs following meningioma diagnosis, 661 (40%) were anxiety and 681 (42%) were depression. The remainder were those with a mixed diagnosis or substance misuse disorder.

Univariate analysis was then performed for the subset of patients who did not carry a preexisting MHD diagnosis to determine factors related to developing an MHD in the setting of a newly diagnosed, untreated meningioma (Table 3). Of note, those patients who developed an MHD after meningioma diagnosis were more likely to be female (78.22% vs 71.14%, *P* < .001), younger (*P* = .013), smokers (11.71%

vs 7.98%, *P* < .001), or to have a history of alcohol abuse (2.50% vs 1.45%, *P* = .004). Furthermore, patients who developed an MHD were more likely to have presented with headaches (5.84% vs 8.66%, *P* < .001) or nonspecific neurological complaints (7.67% vs 9.58%, *P* = .011) and have higher Charlson Comorbidity Index scores (*P* = .001). We subsequently separated those patients diagnosed with depression and those diagnosed with anxiety and performed univariate analyses on these subgroups (Table 4). As seen with the combined cohort, these results revealed female sex, smoking history, and presenting symptoms (headache, vertigo, and nonspecific neurological symptoms) to be associated with the development both of anxiety and depression. Rural area of residence was associated with a higher chance of depression, whereas urban residence was associated with a higher chance of anxiety.

In multivariable analysis (Figure 1), patients who developed MHD were more likely to be female (aOR 1.49; CI, 1.31-1.70), have a smoking history (aOR 1.5; CI, 1.26-1.78), or alcohol history (aOR 1.77; CI, 1.22-2.55). Additionally, patients who developed an MHD were more likely to have presented with headaches (aOR 1.42; CI, 1.17-1.74), nonspecific neurologic symptoms (aOR 1.25; CI, 1.04-1.52), or to have a higher Charlson Comorbidity Index score (aOR 1.33; CI, 1.15-1.54). Of these factors, history of alcohol abuse carried the strongest association with the development of an MHD. Geographic setting, community type, and age did not have any significant effect on the odds of developing an MHD. These findings support the results of the univariate analysis. Multivariable analysis of depression and anxiety subgroups aligned with the results of the larger MHD group with a few notable differences. Female sex (aOR 1.64; CI, 1.35-2.00 and aOR 1.46; CI, 1.21-1.76, respectively) and Charlson Comorbidity Index (aOR 1.30; CI, 1.05-1.60 and aOR 1.36; CI, 1.10-1.68, respectively) were associated with increased risk for development both of anxiety and depression. The depression subgroup analysis did reveal a significant association with smoking (aOR 1.52; CI, 1.18-1.95) and headaches (aOR 1.551; CI, 1.17-2.05) that was not seen in the anxiety subgroup.

**Table 2.** Baseline Characteristics of Patients With Untreated Meningiomas

Characteristic	Variable	n (%)
Residence	Rural	2233 (14.58)
	Urban	13087 (85.42)
Age, y	18-34	918 (5.99)
	35-44	2142 (13.98)
	45-54	5106 (33.33)
	55-65	7154 (46.70)
Sex	Male	3643 (23.78)
	Female	11677 (76.22)
Region	South	5899 (38.51)
	West	2768 (18.07)
	Midwest	3751 (24.48)
	Northeast	2701 (17.63)
	Unknown	201 (1.31)
Smoking	Yes	1511 (9.86)
	No	13809 (90.14)
Alcohol abuse	Yes	343 (2.24)
	No	14977 (97.76)
Presenting symptom	Headache	1225 (8.0)
	Seizures	739 (4.82)
	Visual Symptoms	799 (5.22)
	Vertigo	1660 (10.84)
	Hemiplegia	60 (0.39)
	Nonspecific	1412 (9.22)
Preexisting mental health disorder	Yes	5132 (33.50)
	No	10188 (66.50)

## Discussion

In this large, retrospective study, we found that in patients diagnosed with an untreated meningioma, approximately 16% were diagnosed with an MHD within 1 year of the diagnosis of meningioma. Independent risk factors included female sex and substance misuse. Headaches, nonspecific neurologic symptoms, and higher Charlson Comorbidity Index scores were also independently associated with a subsequent diagnosis of MHD. On subgroup analysis, patients with depression were more likely to have a history of smoking and to have presented with headaches; however, these risk factors were not observed to be significant in the anxiety subgroup.

Mental health disorders are a major public health problem in the United States and globally.<sup>19</sup> Estimated costs for depression alone exceeded \$200 billion in the United States in 2010<sup>20</sup>. Furthermore, the incidence and prevalence of MHDs are increasing.<sup>21</sup> Well-established risk

**Table 3.** Univariate Analysis of Patients With Untreated Meningiomas

Characteristic	Variable	No MHD n (%)	Developed MHD n (%)	P
Residence	Rural	1205 (14.10)	236 (14.40)	.757
	Urban	7344 (85.90)	1403 (85.60)	
Age, y	18-34	568 (6.64)	119 (7.26)	.013
	35-44	1205 (14.10)	278 (16.96)	
	45-54	2843 (33.26)	528 (32.21)	
	55-65	3933 (46.01)	714 (43.56)	
Sex	Male	2467 (28.86)	357 (21.78)	< .001
	Female	6082 (71.14)	1282 (78.22)	
Region	South	3265 (38.19)	653 (39.84)	.322
	West	1471 (17.21)	299 (18.24)	
	Midwest	2075 (24.27)	370 (22.57)	
	Northeast	1616 (18.90)	291 (17.75)	
	Unknown	122 (1.43)	26 (1.59)	
Smoking	Yes	682 (7.98)	192 (11.71)	< .001
	No	7867 (92.02)	1447 (88.29)	
Alcohol abuse	Yes	124 (1.45)	41 (2.50)	.004
	No	8425 (98.55)	1598 (97.50)	
Presenting symptom	Headache	499 (5.84)	142 (8.66)	< .001
	Seizures	373 (4.36)	71 (4.33)	1.000
	Visual symptoms	453 (5.30)	92 (5.61)	.590
	Vertigo	831 (9.72)	166 (10.13)	.618
	Hemiplegia	27 (0.32)	9 (0.55)	.168
	Nonspecific	656 (7.67)	157 (9.58)	.011
Charlson Comorbidity Index score	0	5614 (65.57)	1008 (61.50)	.001
	1	1562 (18.27)	312 (19.04)	
	≥ 2	1373 (16.06)	319 (19.46)	

**Abbreviation:** MHD, mental health disorder.

factors for the development of an MHD include low self-esteem, substance misuse, past trauma, low education, and poor social support.<sup>22</sup> Furthermore, stressful life events are associated with an increased risk of developing MHDs.<sup>23</sup>

Naturally, it follows that the diagnosis of a malignant neoplasm of the CNS, an event that carries a substantial amount of personal stress, is associated with a high risk of developing an MHD. A review by Rooney et al of 4089 glioma patients found between 6% and 28% of patients screen positive for depression.<sup>8</sup> Similarly, a recent large review by Huang and colleagues found 21.7% of brain tumor patients had depression or depressive symptoms.<sup>9</sup> Further studies in this group have placed rates of anxiety between 30% and 60%.<sup>10-13</sup>

Other studies have demonstrated significant differences in MHDs between patients with malignant and benign CNS neoplasms. Mainio et al found that although anxiety is initially high in patients following the diagnosis of a benign meningioma, this anxiety normalizes within 5 years.<sup>24</sup> Further, rates of depression appear to increase over time in those with a malignant glioma, but not with histologically benign neoplasms.<sup>17,25</sup> These differences can be attributed to the often-grim prognosis of malignant entities, demands of treatment, and frequent decline in neurologic function.

Meningiomas carry a far more favorable prognosis, and the burden of treatment is often less demanding. However, because meningioma is the most frequently diagnosed primary CNS neoplasm, the potential burden

of concurrent MHDs may be significant. Here, we found approximately 16% of patients with newly diagnosed, untreated meningiomas developed an MHD. This finding is in keeping with previous small series examining the relationship between MHDs and meningioma. Goebel and Mehdorn<sup>10</sup> examined 52 patients undergoing neurosurgical treatment for meningioma and found that 20% screened positive for anxiety after their diagnosis and 8% for depression. However, the rate of anxiety dropped to 10% following surgery, suggesting at least part of their anxiety was related to their upcoming surgical treatment.

In Goebel and Mehdorn,<sup>10</sup> the authors found that rates of anxiety and depression were similar to the general German population from which the cohort was pulled. Similarly, our own cohort reflects the prevalence of MHDs in the US population. We found that close to one-third (33.5%) of our cohort had an MHD diagnosis prior to the meningioma diagnosis. Large US population studies have observed a lifetime prevalence of depression and anxiety to be approximately 29% (18% and 11%, respectively<sup>20,26,27</sup>). This may not be universal because a recent study from Thurin et al focusing on return to work following meningioma surgery in the Swedish population found that premorbid rates of depression were significantly higher in meningioma patients compared to controls (21.3% vs 16.5%,  $P < .001$ ).<sup>28</sup> One should also note a nearly 8% increase in history of depression at the time of surgery compared to 1 year prior, which is in line with our

**Table 4.** Univariate Analysis of Anxiety and Depression Subgroups in Patients With Untreated Meningiomas

Characteristic	Variable	No MHD		Developed anxiety		P	Developed depression		P
		No.	%	No.	%		No.	%	
Residence	Rural	1205	14.10	85	12.86	.032	103	15.12	.034
	Urban	7344	85.90	576	87.14		578	84.88	
Age, y	18-34	568	6.64	39	5.90	.014	54	7.93	.252
	35-44	1205	14.10	123	18.61		101	14.83	
	45-54	2843	33.26	216	32.68		204	29.96	
	55-65	3933	46.01	283	42.81		322	27.28	
Sex	Male	2467	28.86	133	20.12	< .001	149	21.88	< .001
	Female	6082	71.14	528	79.88		532	78.12	
Region	South	3265	38.19	240	36.31	.892	290	42.58	.146
	West	1471	17.21	121	18.31		119	17.47	
	Midwest	2075	24.27	162	24.51		145	21.44	
	Northeast	1616	18.90	128	19.36		115	16.89	
	Unknown	122	1.43	10	1.51		11	1.62	
Smoking	Yes	682	7.98	67	10.14	.009	79	11.60	< .001
	No	7867	92.02	594	89.86		602	88.40	
Alcohol abuse	Yes	124	1.45	12	1.82	.093	11	1.62	.119
	No	8425	98.55	649	98.18		670	98.38	
Presenting symptom	Headache	499	5.84	49	7.41	.017	62	9.10	< .001
	Seizures	373	4.36	27	4.08	.076	28	4.11	.076
	Visual symptoms	453	5.30	37	5.60	.066	31	4.55	.052
	Vertigo	831	9.72	71	10.74	.037	60	8.81	.041
	Hemiplegia	27	0.32	3	0.45	.201	6	0.88	.022
	Nonspecific	656	7.67	61	9.23	.021	67	9.84	.008
Charlson Comorbidity Index score	0	5614	65.57	419	63.39	.084	406	59.62	.004
	1	1562	18.27	114	17.25		139	20.41	
	≥ 2	1373	16.06	128	19.36		136	19.97	

**Abbreviation:** MHD, mental health disorder.

findings that meningioma diagnosis can have an impact on diagnosis of MHDs.

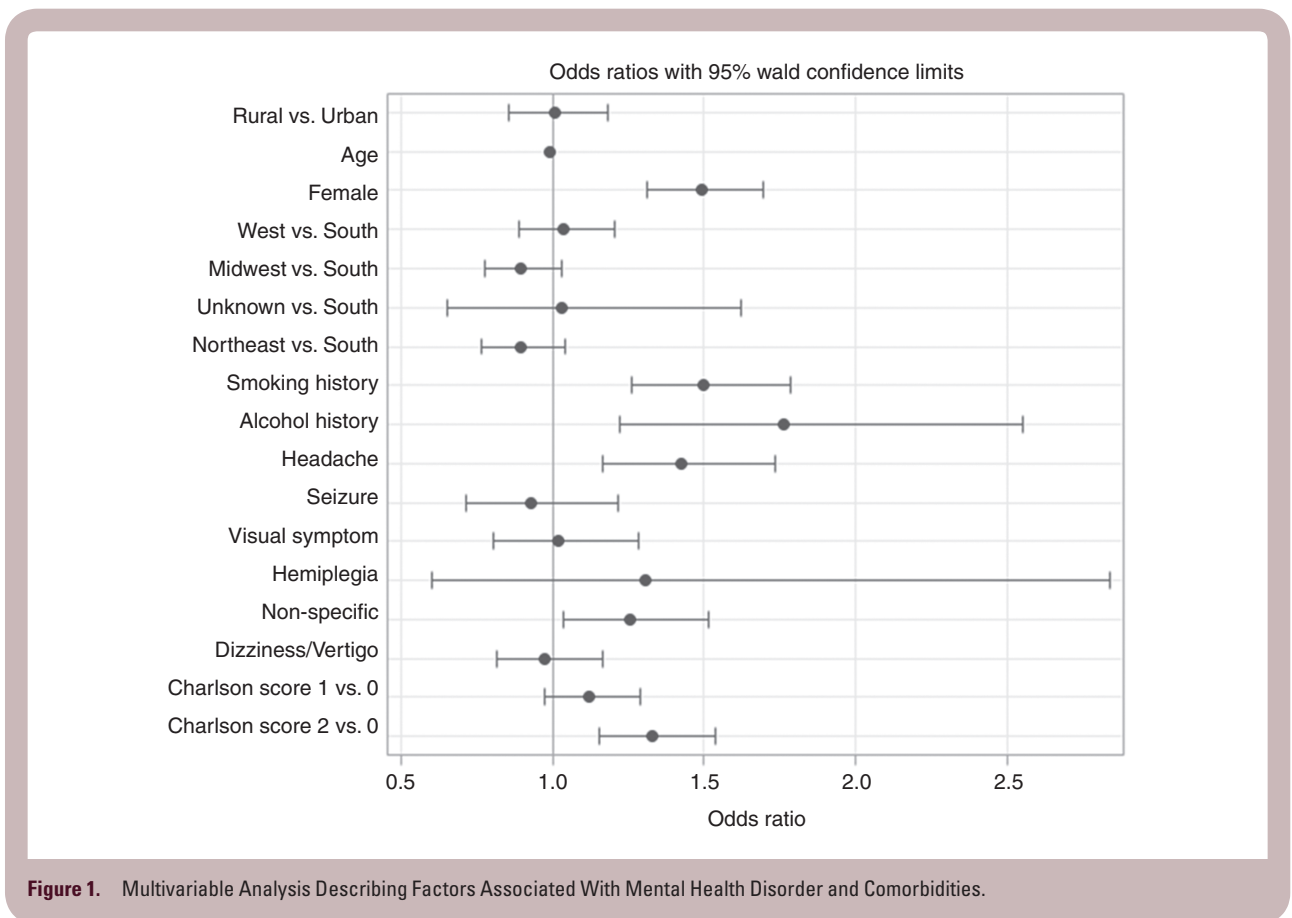
Characteristics identified in our study with increased odds of developing an MND included female sex and history of alcohol or tobacco use. This is not surprising given these variables are associated with increased prevalence of MHDs in the general population.<sup>22,29-32</sup> Recent data further underscore the role of MHD, specifically depression, in return to work and long-term quality of life in patients with meningioma.<sup>28</sup> Understanding the prevalence of MHD development following meningioma diagnosis and appreciating patient and tumor factors associated with a higher risk of MHD development will be of importance when considering screening and survivorship protocols. Incorporation of generic depression and anxiety batteries and early referral to mental health practitioners could be considered in the highest-risk groups.

Interestingly, patients presenting with symptoms of headache and nonspecific symptoms had a higher likelihood of developing an MHD in multivariable analysis. It is surprising that hemiplegia, often a more debilitating symptom than headaches, was not independently associated with risk of MHD. A consideration was made to include cognitive changes in the symptoms analyzed; however, from previous experience with this data set, it was evident that cognitive changes were notoriously undercoded and therefore the decision was made to forego the inclusion of cognitive changes as a symptom. To our knowledge, no

other study of mental health in brain tumor patients has examined an association between presenting symptom and the odds of developing a subsequent MHD.

Although unable to determine this from a database study such as this, it is feasible that specific individual patient factors related to the tumor and diagnosis may have a profound effect on the likelihood of subsequent MHD. For instance, the psychological effect of counseling provided by the patient's neurosurgeon could have a heavy impact on the patient's outlook about his or her diagnosis. It is entirely conceivable that a young patient with a large meningioma who is counseled that surgery might someday be necessary would have a different psychological burden than an older counterpart with a small meningioma who is counseled that necessary intervention is exceedingly unlikely. Unfortunately, the inherent limitations of this study design make any inference on this possibility impossible but certainly further studies to explore this would be valuable.

The primary limitation of this study is inherent limitations to the MarketScan database. As such, errors in clinical coding may have resulted in inaccurate data. However, given the incentive to maximize billing revenue, it is likely that the coding data is reasonably accurate. Additionally, the MarketScan database captures data only from private payers and therefore information regarding meningioma patients covered by Medicare or Medicaid is not included. Our study may therefore underestimate the true



prevalence of MHDs because of the high prevalence of MHDs in patients of low socioeconomic status. Efforts are under way to address this limitation with a more diverse cohort. Additionally, patients with MHDs underuse mental health services and may not be accurately captured by a claims-based database. Furthermore, we included only depression, anxiety, adjustment disorders, and nonalcohol substance misuse in our query of MHDs and therefore may not have captured patients with diagnoses such as bipolar or primary psychosis. Unfortunately, brain tumor location could not be gleaned from the database and was not included in the analysis. A final limitation is our decision to exclude meningioma patients undergoing treatment. These patients are unavoidably subject to a different set of physiologic and psychosocial stressors, which may skew results given the distinct association pattern between MHDs and meningiomas altogether. Further population-based studies are needed to accurately illustrate the association between MHDs and patient undergoing treatment for meningiomas.

## Conclusion

Our study explores the relationship between MHDs and untreated meningiomas across a large and broad population-based cohort. We found a significant proportion of patients with untreated meningiomas will develop

an MHD. By identifying risk factors, appropriate screening can focus on patients at high risk for the development of an MHD.

## Supplementary material

Supplementary material is available online at *Neuro-Oncology Practice* (<http://nop.oxfordjournals.org/>).

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