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# The management of incidental meningioma: An unresolved clinical conundrum

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**Abstract**

The widespread availability and use of brain magnetic resonance imaging and computed tomography has led to an increase in the frequency of incidental meningioma diagnoses. Most incidental meningioma are small, demonstrate indolent behavior during follow-up, and do not require intervention. Occasionally, meningioma growth causes neurological deficits or seizures prompting surgical or radiation treatment. They may cause anxiety to the patient and present a management dilemma for the clinician. The questions for both patient and clinician are "will the meningioma grow and cause symptoms such that it will require treatment within my lifetime?" and "will deferment of treatment result in greater treatment-related risks and lower chance of cure?." International consensus guidelines recommend regular imaging and clinical follow-up, but the duration is not specified. Upfront treatment with surgery or stereotactic radiosurgery/radiotherapy may be recommended but this is potentially an overtreatment, and its benefits must be balanced against the risk of related adverse events. Ideally, treatment should be stratified based on patient and tumor characteristics, but this is presently hindered by low-quality supporting evidence. This review discusses risk factors for meningioma growth, proposed management strategies, and ongoing research in the field.

**Keywords**

asymptomatic | incidental | management | meningioma

## Meningioma and Incidental Findings

Meningioma constitutes approximately a third of all primary brain tumors and are considered a disease of older adults with a median age at diagnosis of 66 years.[1] Their incidence rate increases with age reaching a rate of 57 per 100,000 in adults over the age of 85.[1] Meningioma demonstrates a female preponderance with a ratio of 2:1.[1] Risk factors for meningioma include ionizing radiation and exposure to high-dose cyproterone acetate (CPA).[2,3] NF2-Schwannomatosis is the most common genetic condition associated with meningioma.[4] In the absence of these risk

factors and tumor-related symptoms, a meningioma can be labeled as being incidental.

### Prevalence of Incidental Findings Including Meningioma

Unexpected anomalies on imaging are common. A meta-analysis of systematic reviews identified the commonest imaging modalities to demonstrate incidental findings as chest computed tomography (CT) (45%), followed by CT colonoscopy (38%), chest magnetic resonance imaging (MRI) (34%), and brain and spine MRI (22% each).[5] In population-based studies, asymptomatic brain infarcts, cerebral aneurysms, and brain tumors were present in 7.2%, 1.8%, and 1.6% of the population, respectively.[6,7] Incidental brain tumors included meningioma (0.9%–1.0%), pituitary adenoma (0.3%), vestibular schwannoma (0.1%–0.2%), and glioma (0.05%–0.1%).[6,7] In a meta-analysis of incidental brain findings (16 studies, 19,559 people), the overall number needed to scan to identify an incidental brain finding was 37 and the prevalence of these findings increased with age.[8] The number needed to scan was 345, 667, 2000, and 3333 for meningioma, pituitary adenoma, glioma, and vestibular schwannoma, respectively.[8]

Meningioma comprise 15% of incidental findings on brain MRI and have a prevalence of 5 per 1000 persons.[8,9] With an increasing population age, their prevalence is likely to increase. Furthermore, incidentally discovered asymptomatic meningioma comprise approximately 20% of those newly diagnosed,[10] and in recent studies of the Surveillance, Epidemiology, and End Results database, 46%–55% of meningioma was diagnosed on imaging alone with no histopathological confirmation.[11,12] Therefore, incidental meningioma pose a considerable workload for neurosurgeons, neuro-oncologists, neurologists, and neuroradiologists.

### Impact of Incidental Findings on Patients

Incidental findings can have a negative impact on patients and those affected have been previously described as Victims of Modern Imaging Technology.[13] In a survey of 471 people affected by an incidental finding, 28.6% reported moderate to severe levels of psychological distress after finding out about their imaging anomaly.[14] This distress typically peaks prior to the initial consultation, but it persists throughout imaging surveillance practice in what's known as "scanxiety."[15] Physical, social, and financial harm may arise because of invasive interventions such as surgery and radiotherapy, which may lead to side effects and have an impact on the patient's social activities and jobs. In the context of incidental brain findings, the offset of these harms against early detection, treatment, and improvement of long-term outcomes is variable. For low-grade glioma, evidence suggests that early surgery improves overall survival.[16,17] For other findings such as cerebral aneurysms, arterio-venous malformations, cavernoma, and meningioma, the debate is still ongoing as to the benefit of treatment for asymptomatic patients.[18–21]

### Economic Impact of Incidental Findings

Incidental findings can have substantial monetary costs from a patient and healthcare provider perspective. In a study of 1,000 French patients who underwent a CT scan in an emergency department, 232 had incidental findings and the cost of investigating these was approximately $2,500 per patient with an incidental finding.[22] In a study of incidental findings on abdominal CT for suspected acute appendicitis, 395 out of 876 (45%) had an incidental finding with an additional expenditure of $155,024 for investigation of these.[23] Incidental findings also increase the length of inpatient stay and a physicians' workload.[24–26] The risk of a clinically relevant incidental finding, such as malignancy, is 0.2%–1%.[27] The trade-off between the costs of incidental findings and the benefit of early discovery of these malignancies is unclear and health economic models are lacking. From a patient perspective, the health economic impact of incidental findings has not been assessed. Nonetheless, psychological distress, increased time as inpatient, and time spent undergoing investigations are likely to impact patients financially.

## The Natural History of Incidental Meningioma

Early incidental meningioma studies aimed to describe the characteristics and patterns of growth. More recent studies have focused on identifying the risk of incidental meningioma growth. These studies are primarily single-center and retrospective in nature. Their design also limits comparison of results in that a definition of meningioma growth or progression is not uniform and invariably assesses absolute or relative changes in tumor size. Moreover, change with relation to time (rate) is not always utilized despite recommendation by the Response Assessment in Neuro-Oncology group.[28]

In the earliest study of the natural history of incidental meningioma, the mean annual relative growth rate (RGR) of 17 tumors was 3.8%/year.[29] Twelve tumors (70.6%) had an annual RGR of less than 5%/year and only 2 (11.8%) demonstrated a growth rate of >15%/year. Absolute growth rates (AGR) are also low. In a study of 41 patients, the average AGR was 0.8 $cm^3$/year.[30] Similar growth velocities were also reported across several other studies (Table 1). Categorizing growth as RGR ≥ 15% in more recent studies, the risk of incidental meningioma growth ranged from 38% to 75%.[31–33] However, this correlates poorly with the small risk of development of symptoms and dismisses 2 features of incidental meningioma. Most of these tumors are less than 10 $cm^3$ at the time of diagnosis. Therefore, a relative change by 15% over the total duration of follow-up (eg 10 years) may yield very little and slow change in the burden of disease.[10,34] Moreover, the pattern of incidental meningioma growth is likely Gompertzian (Figure 1) and it is postulated that the manifestation of symptoms may correlate with the rapid growth phase.[35] Due to this, some studies have focused on identifying the risk of rapid incidental meningioma growth defined as AGR ≥ 2 $cm^3$/year or AGR ≥ 1 $cm^3$/year

**Table 1.** Growth dynamics and risk of symptom development in selected studies of patients with an incidental meningioma

| Authors | Year | Number of patients | Duration of follow-up (months) | AGR | RGR | % symptomatic |
|---|---|---|---|---|---|---|
| Delgado-Lopez et al.[37] | 2021 | 85 | 49[a] | 0.51 $cm^3$/year | 9.2%/year | 4.7 |
| Dresser et al.[39] | 2020 | 120 | 76[b] | 0.23 $cm^2$/year | 13.4%/year | — |
| Brugada-Bellsola et al.[40] | 2019 | 46 | 24–120[c] | 0.45 $cm^3$/year | — | 4.3 |
| Behbahani et al.[38] | 2019 | 64 | 60 | 0.33 $cm^3$/year | — | 0 |
| Oya et al.[41] | 2011 | 154 | 43[b] | 0.68 $cm^3$/year | — | — |
| Nakamura et al.[36] | 2003 | 41 | 43[b] | 0.79 $cm^3$/year | 14.6%/year | — |
| Firsching et al.[35] | 1990 | 17 | 21[a] | — | 3.6%/year | 0 |

**Abbreviations:** AGR, absolute growth rate; RGR, relative growth rate.
[a]Median.
[b]Mean.
[c]Range.

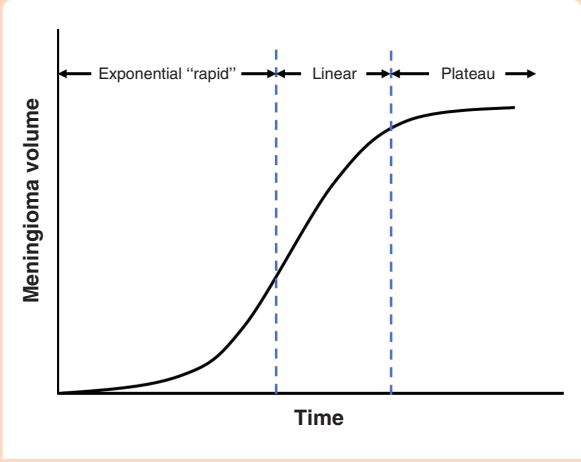


**Figure 1.** Incidental meningioma growth pattern in a Gompertzian model. In this model, a meningioma demonstrates exponential growth in the early stage and linear growth in the intermediate stage before a plateau is finally reached.

and RGR ≥ 30%/year.[10,34] In studies ranging in size from 46 to 441 patients, the risk of this was 7%.[10,36] The risk of a development of new symptoms in patients with an incidental meningioma is 5%–8%.[37,38] All studies to date have investigated the short- and medium-term (up to 10 years) radiological and clinical behavior of incidental meningioma and therefore current understanding of the natural history only aids in decision-making within this time frame.

## Prognostic Features of Incidental Meningioma Growth

### Clinical Features

Several studies have investigated the risk factors associated with the growth of an incidental meningioma. Younger age is associated with growth,[39–41] and although this may be attributed to the longer period of observation these patients may be subject to, a meta-analysis of 27 studies demonstrated age less than 60 was associated with rapid growth.[38] Male sex was shown in 1 study to predispose to a faster growth rate,[40] but this was not evident in other studies.[31–33,39,42] As meningioma often express estrogen receptors, which were linked to a higher proliferative activity *in vitro*,[43] there is a presumed association between estrogen-based hormone replacement therapy (e-HRT) and tumor growth. Conversely, a recent comparative cohort study demonstrated slower meningioma growth in women utilizing e-HRT.[44] The use of high doses of CPA, a progesterone agonist, is associated with the development and growth of meningioma,[2,45] but a similar association is not definite with the use of HRT or oral contraceptives.[46] In view of this association, a diagnosis of meningioma in patients utilizing high doses of CPA should not be considered incidental.

### Imaging Features

The first imaging feature to emerge as a predictor for growth was lack of calcification on CT.[47,48] MRI is often obtained in the diagnosis of meningioma. A hyperintense meningioma signal on T2-weighted (T2-WI) MRI and absence of calcification are highly correlated,[10] and various MRI sequences have been shown to reliably delineate meningioma-related calcification.[49] A hyperintense meningioma signal on T2-WI MRI is now recognized as the feature most predictive of any growth and rapid growth of an incidental meningioma.[30,34,37,38,41] The presence of peri-tumoral signal change indicative of edema is also predictive of growth; however, the presence of this in association with an incidental meningioma is rare.[10,42,50] These 2 features are important to ascertain at the time of diagnosis. Additionally, as progression of calcification may be a marker of growth deceleration,[51] there also may be a role for assessing how these imaging features change over time in relation to volume to inform decision-making. A large tumor volume is predictive of rapid growth.[10,32,50] In

one study, skull base meningioma grew more slowly than nonskull base meningioma.[52] Biologically, this is plausible given the more frequent occurrence of nonmalignant meningioma and genomic stability in comparison to nonskull base tumors[53–56]; however, other studies did not demonstrate such a relationship between location and growth. This may be due to most incidental meningioma being nonskull base and the lower accuracy of measuring skull base meningioma volume using established methods.[37,57] It is also the case that skull base meningioma can transition from asymptomatic to symptomatic without demonstrable growth, for instance visual failure with suprasellar meningioma or optic nerve sheath disease or trigeminal neuralgia with meningioma of the cerebellopontine angle.

The prediction of symptomatic progression of an incidental meningioma has eluded single-center studies owing to its rarity and the small population sizes in these studies.[31–33,36] In meta-analyses, the presence of peritumoral edema and meningioma volume >10 $cm^3$ at diagnosis—features not very commonly associated with an incidental meningioma—was predictors of symptomatic progression.[37,38]

## The Management of Incidental Meningioma

### Active Monitoring

Periodic imaging and clinical assessment after diagnosis of an incidental meningioma is the first-line management option recommended by the European Association of Neuro-Oncology (EANO), National Comprehensive Cancer Network (NCCN), and National Institute for Health and Care Excellence (NICE).[58–61] The intervals for monitoring and duration of follow-up are either undefined or vary considerably, reflecting the lack of informative evidence (Figure 2). In 2 recent meta-analyses,[37,38] meningioma growth mostly occurred within 5 years of diagnosis reaching a plateau thereafter. This would indicate follow-up beyond 5 years may be of little value. Imaging intervals during those years, however, vary across guidelines and if applied, could miss cases of rapid meningioma growth or symptom development. After a 1 year scan, in the UK, NICE recommends a further scan at 5 years or cessation of follow-up, but rapid growth and symptom development have been reported to occur after median follow-up periods ranging from 24 to 33 months.[10,50] This highlights another disadvantage of these guidelines, which is the lack of a personalized monitoring approach tailored to each patient's characteristics and meningioma features. To overcome these limitations prognostic models have been developed. The ***A***san ***I***ntracranial ***M***eningioma ***S***coring ***S***ystem (AIMSS) was created with the aim of estimating a personalized risk of rapid growth and informing "wait and see" strategies accordingly.[50] The scoring tool included the absence of meningioma calcification and a hyperintense meningioma signal on T2-WI MRI. The ***I***ncidental ***M***eningioma: ***P***rognostic ***A***nalysis Using Patient ***C***omorbidity and MRI ***T***ests (IMPACT) calculator (https://www.impact-meningioma.com/) stratified patients based on MRI parameters: meningioma volume, meningioma signal intensity on T2-WI and/or fluid attenuated inversion recovery MRI, peri-tumoral signal change and location in addition to clinical features such as comorbidity and functional status. Both scoring systems need to be validated but may serve as a guide to help clinicians and patients agree an appropriate follow-up plan (Figure 3).

### Upfront Intervention

Several studies recommend upfront treatment of an incidental meningioma.[41,62–64] This is due to factors including uncertainty surrounding the long-term outcomes (beyond 10 years), location, proximity to critical neurovascular structures that would impede safe surgery if growth were to occur, and the chance of missing the window for stereotactic radiosurgery (SRS) if volume exceeds 10 $cm^3$. In a study of 201 patients with <3 cm meningioma, of whom 102 were asymptomatic, the overall

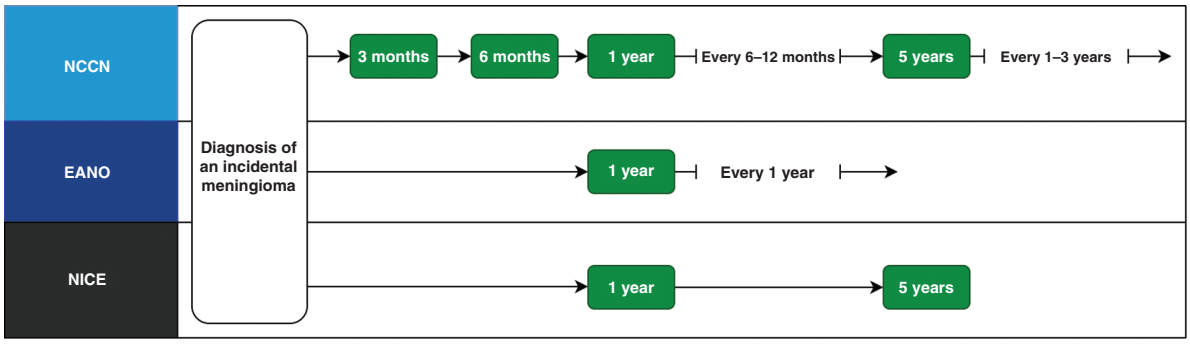


**Figure 2.** Active monitoring recommendations for the management of patients with an incidental meningioma. Time points in boxes are suggested time intervals for scans. Annotated arrows describe further imaging intervals between or after the main imaging intervals in the boxes.

risk of permanent neurological morbidity was 4.9% in asymptomatic patients compared to 23.2% in symptomatic patients.[62] The authors concluded surgery may be considered as first-line management choice. After matching for patient age, tumor location, and extent of resection, another study demonstrated patients with an asymptomatic tumor had a similar risk of side effects, such as seizure (7%) and a new or worsening neurological deficit (9%), 1 year after surgery.[65] In a meta-analysis, histopathological grading of an incidental meningioma often showed WHO grade 1 meningioma (94%).[37]

Upfront treatment with SRS is an appealing option given the excellent local control rates (98%–99%), and the low risk of permanent side effects (2.5%–3%).[21,41] The ***I**ncidental **M**eningioma **P**rogression During **A**ctive **S**urveillance or After **St**E**r**eotactic Radiosurgery (IMPASSE) international multicenter study compared outcomes of 311 patients treated with SRS, matched based on age, tumor volume, location, and duration of imaging follow-up to a cohort of patients actively monitored.[21] After a median of approximately 5 years, radiological tumor control was improved in patients who were treated with SRS (99.4% vs 62.1%). However, this did not translate into a reduction in the risk of symptom development (~3% in both cohorts). Interestingly risk factors for development of an adverse event after SRS treatment include a larger meningioma volume and the presence of peri-tumoral edema; factors that also predispose to meningioma growth.[41,64,66]

## Quality of Life and Neurocognitive Function Outcomes

A 2019 meta-analysis included only two studies examining quality of life (QoL) and neurocognitive function (NCF) with conflicting results on the negative impact of an incidental meningioma.[37] More recently, a population-based study demonstrated approximately a quarter of patients developed depression 1 year after diagnosis. This was related to factors such as female sex and substance misuse but it was unclear whether this would have manifested regardless of the meningioma diagnosis.[67] In a matched cross-sectional cohort study, the prevalence of anxiety in patients actively monitored was similar to patients after surgery for a meningioma (42%, $P = .60$), yet depression was more common (61% vs 87%, $P = .005$). General health and its constituent physical component scores were worse in patients undergoing active monitoring.[68] In patients treated surgically, studies have demonstrated cognitive difficulties, emotional and social dysfunction, sleep disorders, and fatigue in the longer term.[69,70] No studies have examined the impact of SRS on QoL and NCF in incidental meningioma patients.

## Decision-making—Upfront Intervention Versus Active Monitoring

Considering the similar risk of side effects of surgery for an asymptomatic meningioma to a symptomatic meningioma and the low likelihood of a grade 2 or 3 meningioma, upfront surgery for all patients with an incidental meningioma is not indicated and is reserved for symptomatic or growing tumors. With regards to SRS, for patients at low risk of demonstrating meningioma growth, the use of SRS may be safe at least in the short to medium term, but probably unnecessary. Patients at high risk of meningioma growth and development of symptoms are also those who may experience SRS-related side effects. For these patients, the decision to offer early SRS or to observe may depend on the nature of any resulting side effects/new symptoms and the timing at which this will be tolerable from a patient perspective and preference. In terms of maintaining a meningioma within the safe SRS and surgery windows, the recent prognostic models have incorporated relevant endpoints toward advising monitoring protocols, however, these are yet to be validated.[10,34] With regards to QoL and NCF, it is clear that psychosocial support may be required for patients with an incidental meningioma and therefore it may be reasonable that they should have a named clinical nurse specialist to aid with this. It remains unclear how management decisions should be shaped in view of QoL and NCF literature results.

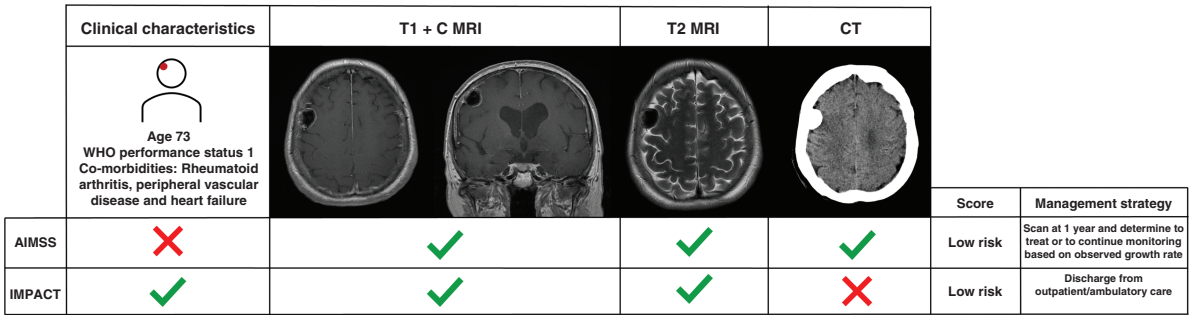


**Figure 3.** Examples of the utility of IMPACT and AIMSS scoring systems in devising a management strategy for incidental meningioma.

## Ongoing Research in Incidental Meningioma

### External Validation of IMPACT

Whilst the internal validity of personalized active monitoring models has been adequate, neither IMPACT nor AIMSS has been tested in independent cohorts of patients with an incidental meningioma to assess their external validity.[10,50] An international multicenter study is currently ongoing to assess the external validity of IMPACT in 38 centers across 17 countries.[71] The study will aim to collect data for 1,500 patients with an incidental meningioma, powered to detect a 10% progression risk. Adult patients aged ≥16 years diagnosed with an incidental meningioma between 1 January 2009 and 31 December 2010 will be included. The study endpoint is a composite combining clinical progression, rapid growth, and radiological measures of loss of safe surgery and SRS. As of March 13, 2022, data for 735 patients have been collected and the study is expected to close 2022.

### COSMIC: Observation

Studies of incidental meningioma have to date focused on their radiological behavior and recommended management options based on this. Definitions of growth vary and reporting of endpoints such as clinical progression, loss of safe SRS and surgery windows, and requirement for intervention are inconsistently reported. It is unclear which of these endpoints, if any, matter to patients, and studies comparing interventions lack assessment of QoL and NCF. The prospect of treatment arm stratification based on clinical and imaging features exists. Prior to designing prospective studies to assess this, it is imperative to assess which outcomes matter to all stakeholders including clinicians and patients. Stratification based on baseline features brings a difficulty in recruitment of a sufficient number of patients into treatment arms. For instance, if stratification is by a single imaging feature, such as peri-tumoral edema, this is only present in 5% of patients, which therefore limits its utility.[10] For this reason, meaningful comparison across studies to determine comparative efficacy must measure uniform outcomes. Core outcome sets (COS) are gaining momentum in overcoming these challenges. A COS is defined as the minimum set of outcomes that should be measured and reported in all clinical trials for a specific condition or health area.[72] The "***C***ore ***O***utcome ***S***ets" for ***M***eningioma ***I***n ***C***linical Studies (COSMIC) project (https://www.thecosmicproject.org/) is an international multidisciplinary initiative that will use systematic reviews and consensus methodology to develop COS for clinical effectiveness trials (COSMIC: Intervention), and clinical studies of incidental/untreated intracranial meningioma (COSMIC: Observation).

## Future Directions and Recommendations

### Unanswered Questions

Blood biomarkers of meningioma grades and subtypes have been developed, such as Fibulin-2 and DNA methylation state.[73,74] The utility of these in prognostication of incidental meningioma growth and development of symptoms is yet to be determined. Most incidental meningioma that undergo surgery are WHO grade 1 tumors with no cases of recurrence observed in a meta-analysis.[37] Therefore, the association of these biomarkers with growth behavior of an untreated meningioma needs to be tested. Information from these biomarkers may be combined with other prognostic information similar to other machine-learning models developed for classification and prognostication of operated meningioma.[75,76] The health economic impact of treatment decision-making for patients with an incidental meningioma is an area that has not been explored. Health economic models assessing upfront treatment versus active monitoring are needed; however, this requires assessment of QoL at various disease points (diagnosis, progression, and intervention). Such models could also be stratified based on the baseline clinical and imaging features to aid decision-making for the group of patients who are likely to require intervention for disease progression at some point during follow-up. The prospect of a clinical trial of intervention (eg SRS) versus observation for all patients with an incidental meningioma has been recommended as an area for future research.[77] There may be, however, a lack of clinical equipoise and inherent bias in decision-making by patients and clinicians, as approximately 90% of patients with incidental meningioma do not require or receive intervention during the first 5–10 years of follow-up. Instead, risk stratified clinical trials may be an option; patients with meningioma at high risk of progression—eg a hyperintense meningioma signal on T2-WI MRI with peri-tumoral edema (Figure 4)—may benefit from an intervention trial, whereas patients with low- or medium-risk incidental meningioma may draw more benefit from studies that compare different monitoring strategies.

### Recommendations for Practice

- Active monitoring should be considered the first-line management strategy in patients with an incidental meningioma. Duration of follow-up and intervals for monitoring may be informed by prognostic models such as AIMSS and IMPACT. These remain to be externally validated.
- Early intervention for patients at high risk of progression may be considered. Features that would suggest a high risk include a hyperintense meningioma signal on T2-WI MRI, volume >10 $cm^3$ and peri-tumoral edema.
- First line therapeutic intervention may be SRS or surgery in case of incidental meningioma; the majority are eligible for SRS (<10 $cm^3$). In cases of progression despite SRS (1% risk[21]) or when SRS is contra-indicated (volume > 10 $cm^3$), surgery may be considered.
- There should be shared decision-making with the pros and cons discussed such that informed patient preference for treatment can be achieved for all 3 management options (active monitoring, surgery, and SRS). It

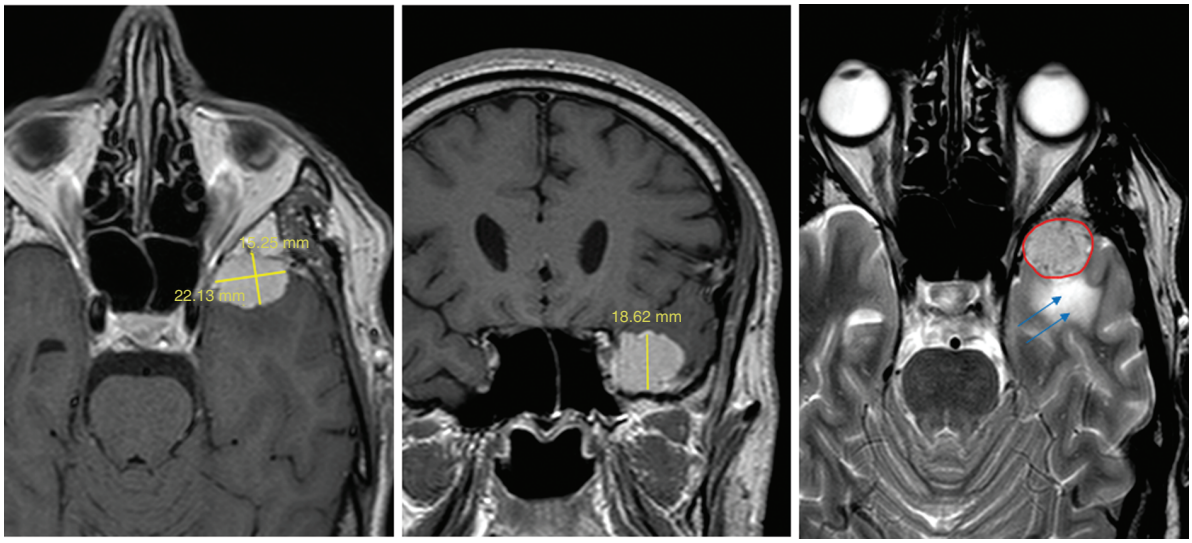


**Figure 4.** A left-sided sphenoid wing meningioma. Volume at diagnosis was 3.14 $cm^3$. There was evidence of peritumoural signal change (two arrows) and a hyperintense signal on T2-WI MRI (circle). Using the IMPACT calculator, this meningioma could be classified as high risk.

may be reasonable that all patients with incidental meningioma should have a named clinical nurse specialist to manage expectations at outset, define the role of MRI monitoring and reduce the anxiety associated with surveillance scans (scanxiety).

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