

Abstract

Introduction

There are a number of prognostic markers (methylation, CDKN2A/B) described to be useful for the stratification of meningiomas. However, there are currently no clinically validated biomarkers for the preoperative prediction of meningioma grade, which is determined by the histological analysis of tissue obtained from surgery.

Accurate preoperative biomarkers would inform the pre-surgical assessment of these tumours, their grade and prognosis and refine the decision-making process for treatment. This review is focused on the more controversial grade II tumours, where debate still surrounds the need for adjuvant therapy, repeat surgery and frequency of follow up.

Methods

We evaluated current literature for potential grade II meningioma clinical biomarkers, focusing on radiological, biochemical (blood assays) and immunohistochemical markers for diagnosis and prognosis, and how they can be used to differentiate them from grade I meningiomas using the post-2016 WHO classification. To do this, we conducted a PUBMED, SCOPUS, OVID SP, SciELO, and INFORMA search using the keywords; 'biomarker', 'diagnosis', 'atypical', 'meningioma', 'prognosis', 'grade I', 'grade 1', 'grade II' and 'grade 2'.

Results

We identified 1779 papers, 20 of which were eligible for systematic review according to the defined inclusion and exclusion criteria. From the review, we identified radiological characteristics (irregular tumour shape, tumour growth rate faster than 3cm³/year, high peri-tumoural blood flow), blood markers (low serum TIMP1/2, high serum HER2, high plasma Fibulin-2) and histological markers (low H3K27me3, low SMARCE1, low AKAP12, high ARIDB4) that may aid in differentiating grade II from grade I meningiomas

Conclusion

Being able to predict meningioma grade at presentation using the radiological and blood markers described may influence management as the likely grade II tumours will be followed up or treated more aggressively, while the histological markers may prognosticate progression or post-treatment recurrence. This to an extent offers a more personalised treatment approach for patients.

Introduction

Meningiomas are common primary tumours of the central nervous system (CNS). Recent data suggest that they constitute up to 30% of all intracranial tumours (Norden et al. 2007, Gupta et al. 2017), have a 1% incidence rate on routine magnetic resonance imaging (MRI) (Laukamp et al. 2019), with about a third of cases having high recurrence rates despite optimum treatment (Magill et al. 2020).

Histological analysis remains the gold standard for diagnosis. Imaging offers a high (not absolute) degree of diagnostic certainty, but with a range of differential diagnoses (e.g. metastases, gliosarcomas, haemangiopericytomas) that radiologically mimic meningiomas, and potentially complicate management (Erkan et al. 2019, Goldbrunner et al. 2016).

According to the most recent (2016) World Health Organization classification of tumours of the central nervous system (Louis et al. 2016), there are three distinct histological tumour grades that predict likely tumour behaviour and prognosis (Laukamp et al. 2019); benign grade I meningiomas (70 - 85% of all meningiomas), more aggressive grade II (15 – 30% of all meningiomas) and the most aggressive anaplastic grade III tumours (1 - 5%) (Backer-Grøndahl et al. 2012, Harmancı et al. 2017).

Due to the diverse morphological characteristics of meningiomas (Ülgen et al. 2019), their WHO histological diagnostic criteria is complex (Louis et al. 2016), especially with the grade II tumours where inter observer discordance can be as high as 12.2%, compared to 7% and 6.4% in grade I and III tumours respectively (Harter et al. 2017, Rogers et al. 2016). Grade II tumours have highly heterogeneous histological properties (Katz et al. 2018) and can behave on a biological spectrum similar to the grade I or III tumours with unpredictable clinical courses (Zhang et al. 2019, Katz et al. 2018), while clinically aggressive grade I meningiomas (defined by recurrence and disease progression requiring treatment within 10 years) can also have clinical courses similar to the grade II tumours (Parada et al. 2020). This suggests that using histological grade in isolation is not the best predictor of the clinical course of these clinically aggressive grades I or II meningiomas, and that we need to identify biomarkers to supplement and refine the current WHO grading system. The proliferation index, Ki67 is an example of a known immunohistochemical meningioma prognostic biomarker, with higher indices associated with poorer survival and higher meningioma grade (Liu et al. 2020, Hirato et al. 1996, Harter et al. 2017). However, the correlation with recurrence or disease progression remains unclear with conflicting evidence in literature (Tyagi et al. 2004, Haddad et al. 2020, Li et al. 2019, Zhang et al. 2019). DNA methylation-based meningioma classification has been recently shown to supplement histologically grade and improve the accuracy of predicting risks of progression and/or recurrence (Sahm et al. 2017; Suppiah et al., 2019).

Grade II meningiomas are controversial with regards their management and diagnosis (Rogers et al. 2016, Jenkinson et al. 2016, Harter et al. 2017, Sherratt et al. 2020, Goldbrunner et al. 2016), as demonstrated by the inclusion of brain invasion as a major criterion for diagnosis in the 2016 WHO classification; a criterion with evidence both supporting and disputing the relevance to survival and disease recurrence (Barresi et al. 2018, Barrett et al. 2019, Budohoski et al. 2018, Nowak et al. 2015, Sun et al. 2014b, Kim et al. 2018, Vranic et al. 2010, Hardesty et al. 2013, Endo et al. 2016).

The initial management of symptomatic meningiomas is relatively straightforward (treated with surgery or radiotherapy irrespective of grade (Magill et al. 2018), but there is a lack of general consensus/uniformity with regards the optimum overall management. While there are ongoing clinical trials (ROAM/EORTC-1308, NRG-BN003 and RTOG-0539) investigating this (Jenkinson et al. 2015, Rogers et al. 2020, Sherratt et al. 2020, Rogers et al. 2016, Rogers et al. 2018, Fleming et al. 2018, BN003 2018), there is currently no clear evidence for the role of adjuvant radiotherapy, the frequency or duration of follow up, (Budohoski et al. 2018, Sun et al. 2014a, Jenkinson et al. 2015) of the grade II tumours. Therefore, regional institutional multidisciplinary neuro-oncology teams make management decisions based on their historical practice (Katz et al. 2018). These factors also contribute to the controversy around the management of grade II meningiomas.

Recent meningioma genomics studies have revealed extensive molecular heterogeneity, especially in the higher-grade tumours, that include; the familial germline mutation seen in monosomy 22/NF2 syndrome where ~70% of patients with the syndrome develop multiple meningiomas, the loss/inactivation of the NF2 gene in ~60% of sporadic meningiomas and the homozygous deletion of CDKN2A/B in clinically aggressive meningiomas (Suppiah et al., 2019). Other meningioma driver mutations identified by next generation DNA sequencing to be exclusive of NF2 mutations (and enriched in grade I meningiomas) include; TRAF7 mutations in 12-25% of all meningiomas, AKT1 mutations in 5-9% of meningiomas, KLF4 mutations in 9% of meningiomas, and the rarer mutations in PIK3CA (3-4% of all meningiomas), SMO (1-5%) and POLR2A (6%) (Abbritti et al., 2016; Brastianos et al., 2013; Clark et al., 2013; Clark et al., 2016; Nigim et al., 2018; Suppiah et al., 2019).

With the increasing emphasis on an integrated molecular approach to managing central nervous system (CNS) tumours (Louis et al. 2016, Nowosielski et al. 2017), there is the potential for biomarkers to aid the diagnosis, management, and prognosis of meningiomas, similar to recent developments in the management of gliomas.

We aim to evaluate and summarise the current (post 2016) literature for grade II meningioma versus grade I clinical biomarker differences, focusing on radiological and biochemical (blood-based assays) markers for pre-operative diagnosis, and histological/immunohistochemical markers for post-

operative prognosis. This review describes biomarkers with potential clinical applications in the management of this subset of meningiomas, potentially guiding the neuro-oncology multidisciplinary team and informing patients. This has potential implications for managing healthcare resources by using these biomarkers to predict which patients will need closer follow-up and/or imaging surveillance, based on the suspicion of a non-benign meningioma.

Methods

Literature Review

We performed a systematic review of the literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria by searching the PubMed, SciELO, Scopus, and Ovid databases (Osunronbi et al. 2020; Moher et al., 2009), to identify articles describing biomarker differences between grade I and II meningiomas, up to and including February 2020. The following search keywords were used in different combinations: 'biomarker', 'diagnosis', 'atypical', 'meningioma', 'prognosis', 'grade I', 'grade 1', 'grade II' and 'grade 2'. Reference lists of identified articles were searched for other potential papers for inclusion [insert PRISMA chart].

This combination of keywords generated 1779 articles once duplicates were removed. These articles' abstracts and titles were then screened for relevance yielding 207 articles.

Inclusion and exclusion criteria

For inclusion, the published article must:

- (i) describe at least one biomarker specifically related to grade II meningiomas
- (ii) be written in/translated to the English language.
- (iii) classify/grade the meningiomas according to the 2016 WHO classification

Articles describing non-grade specific meningioma biomarkers, and papers that used pre 2016 WHO classifications to grade their meningiomas were excluded because of the significant and relevant revisions in the 2016 version (Louis et al. 2016), with regards the diagnosis of grade II meningiomas. Reviewer's comments, animal studies and non-English articles were also excluded.

20 articles met the above inclusion/exclusion criteria and were included in the final analysis.

Literature review

Radiological biomarkers

Fifteen (75%) of the twenty papers reviewed discussed radiological characteristics of grade II meningiomas. The main MRI sequences reported to predict tumour grade were T1 weighted, T2 weighted, Fluid-attenuated inversion recovery (FLAIR), Apparent Diffusion Coefficient (ADC), Diffusion Weighted Imaging (DWI), Intra-voxel incoherent motion diffusion coefficient (D value), arterial spin labelling and T1.gad (T1-weighted gadolinium enhanced). MRI scanners with a field strength of either 1.5 or 3 Tesla were used in these studies.

Descriptors such as shape, contrast enhancement, peri-tumoural oedema (Adeli et al. 2018) and texture of the tumours on MRI were significant biomarkers for differentiating grade II from grade I meningiomas, while T1 and T2 weighted MRI sequences were unable to predict meningioma grade (Laukamp et al. 2019). Grade II meningiomas have a less uniform/spherical shape on FLAIR when compared to grade I tumours (AUC 0.8, sensitivity 67%, specificity 87%). Tumour texture was determined by measuring the cluster shades of FLAIR/T1.gad-gray-level (lower in grade II, AUC 0.8, sensitivity 58%, specificity 89%), the FLAIR/T1.gad-gray-level-energy (higher in grade II, AUC 0.76, sensitivity 75%, specificity 78%) and the DWI-ADC-gray-level-variability (lower in grade II, AUC 0.72, sensitivity 50%, specificity 89%); indicating a more heterogeneous grade II tumour texture/consistency when compared to grade I tumours (Laukamp et al. 2019, Zhu et al. 2019, Park et al. 2019), and higher levels of intra-tumoural necrosis in the grade II meningiomas (Laukamp et al. 2019).

The MRI Intra-voxel incoherent motion diffusion coefficient (D value) was found to be superior to DWI in distinguishing between grade I and II meningiomas. The D value is a measure of cellular density, where a lower coefficient indicates higher cellular density (as in grade II meningiomas) and a higher coefficient indicates lower cellular density, as seen in grade I meningiomas. A cut-off D value of $0.479 \times 10\text{mm}^2/\text{s}$ was consistently able to distinguish between grade I and II meningiomas (Yiping et al. 2017).

Lu et al described the use of MRI arterial spin labelling to differentiate between grade I and II tumours. They showed that the cerebral blood flow within the peri-tumoural oedema is significantly higher in grade II meningiomas ($30.30 \pm 15.56 \text{ ml/min/100g}$ in grade II, versus $22.33 \pm 9.87 \text{ ml/min/100g}$ in grade I meningiomas; $p=0.037$), suggestive of more extensive arachnoid infiltration of the grade II tumours with more aggressive neovascularization (Lu et al. 2018) [insert Table 1].

While the preoperative tumour size (largest diameter measured in the axial, coronal and sagittal planes) did not correlate with histological grade (Spille et al. 2019), volumetric growth rate (already established as a method for assessing growth rate in low-grade gliomas) is higher in grade II meningiomas compared to grade I (Hale et al. 2018), with a growth rate greater than 3cm³/year described as the optimal threshold that distinguishes between grade I and II meningiomas (Soon et al. 2017).

The use of proton magnetic resonance (¹H-MRS) spectroscopy in the diagnosis of gliomas is well established (Balmaceda et al. 2006, Chiang et al. 2018), but the value in the clinical management of meningiomas remains controversial. The Choline/N-acetylaspartate, Cho/NAA ratio was reported as the most significant difference (higher in grade II) between grade I and II meningiomas, with a cut-off value > 2.409 (positive predictive value: 72.7%, negative predictive value: 79.2%) being associated with the higher-grade tumours (Lin et al. 2018).

Joo et al investigated the use of amide proton transfer (APT) weighted MRI for stratifying meningiomas according to grade and reported significantly higher signal intensities in the grade II tumours compared to grade I, with a cut-off value > 2.19 (normalised magnetisation transfer ratio). This observation may be due to the increased cellularity seen in grade II meningiomas (versus grade I), with an associated increase in intracellular protein content (Joo et al. 2018).

Besides MRI, nuclear imaging is a potential modality for diagnosing/staging meningiomas. Mitamura et al assessed the PET uptake of 2-deoxy-2-¹⁸F-fluoro-d-glucose, FDG (9.25 ± 2.16 in grade II, versus 5.76 ± 2.23 in grade I meningiomas; p=0.003) and L-[methyl-¹¹C]-methionine, MET (8.70 ± 2.59 in grade II, versus 5.49 ± 1.02 in grade I meningiomas; p=0.002) and described significantly higher maximum tumour standardized uptake values in the grade II tumours (Mitamura et al. 2018), highlighting the potential use of FDG and MET PET/CT in predicting meningioma grade in a pre-operative setting. However, MET PET/CT has been shown to be superior to FDG PET/CT when assessing for recurrent or residual grade II meningiomas in the post-operative setting (Tomura et al. 2018, Mitamura et al. 2018).

Blood-based biomarkers

Published data on blood biomarkers for differentiating between grade I and II meningiomas are scarce, as the more promising markers only yield significant results when comparing between meningioma and non-meningioma patients, and not between tumour grades. After application of the

inclusion/exclusion criteria, we reviewed three papers (Abtahi et al. 2019, Mashayekhi et al. 2018, Sofela et al. 2021) describing four grade II meningioma blood biomarkers.

Tissue inhibitors of metalloproteinases (TIMPs) limit the degradation of the extracellular matrix (ECM) and basement membrane by their actions as endogenous inhibitors of matrix metalloproteinases (MMPs). ECM degradation is a key stage in the process of tumour invasion and progression, and the downregulation/inactivation of some TIMP genes are known to be associated with higher grade or more aggressive meningioma phenotypes (Barski et al. 2010, Rooprai et al. 2016). TIMP-1 and TIMP-2 serum levels measured by ELISA were significantly lower in grade II meningioma patients compared to levels measured in grade I patients (Mashayekhi et al. 2018). The authors also showed that the serum levels of both TIMPs were lower in a control cohort compared to meningioma patients. These findings suggest that TIMP-1 and TIMP-2 serum levels can be used in combination with the (pre-treatment) radiological findings for prognostication, but not as a post-treatment marker for surveillance as decreasing post-operative serum TIMP-1 or TIMP-2 levels will not clearly differentiate between disease clearance and progression.

Human epidermal growth factor 2 (HER2) is a known proto-oncogene involved in breast malignancies. Abtahi et al demonstrated significantly higher serum levels in grade II meningioma patients compared to grade I (Abtahi et al. 2019). However, in addition to the small grade II sample size (n=7) being a limitation of this study, the authors also acknowledge that other studies (Potti et al. 2004) have not shown a correlation between high expression of HER2 via IHC and tumour grade or prognosis (Abtahi et al. 2019).

We recently published data on Fibulin-2, the calcium binding extracellular matrix glycoprotein, as a novel biomarker difference between grade I and II meningiomas. Plasma Fibulin-2 levels were shown to be significantly higher in grade II (n=47) compared to grade I (n=40) meningioma patients, with a Fibulin-2 plasma concentration cut off value > 2.5ng/ml being 95% specific for identifying patients with grade II meningiomas over those with grade I tumours (Sofela et al. 2021). This study also confirmed that the trend of grade II meningioma Fibulin-2 over-expression observed is similar at both the protein and RNA levels and can serve as a non-invasive biomarker for predicting (pre-operative) grade and prognosticating likely clinically aggressive (histologically confirmed) grade I meningiomas (Sofela et al. 2021). [insert Table 2]

Histological markers

In this section, we discuss five molecular markers (Zhang et al. 2019, Katz et al. 2018, Tauziède-Espariat et al. 2018, Tsai et al. 2017, Parada et al. 2018) that may have potential roles for the post-operative prognostication of grade II meningiomas, by reviewing immunohistochemical studies that described these biomarkers as significantly differentially expressed in grade II meningiomas (compared to grade I), and were associated with increased recurrence, and poorer outcomes on follow up.

Connexin 43, Cx43 expression was observed to be significantly lower in (secondary) grade II meningiomas (Zhang et al. 2019) that progressed from a previously diagnosed benign tumour, compared to primary grade II meningiomas (de novo tumours). Cx43, a gap junction protein previously shown to be distributed in arachnoid villi cell membranes is known to be expressed by meningiomas. The lower expression of Cx43 observed in the secondary (initially benign) grade II tumours may be explained by its previously described tumour-suppressive properties (Zhang et al. 2019).

The evaluation of DNA methylation in meningiomas has been shown by Sahm et al. to improve on the prognostic value of the WHO histological grading, by stratifying grade I and II tumours into different methylation classes (benign 1, 2, 3 and intermediate A & B classes) that correlate better to prognosis compared to the WHO grading alone (Sahm et al. 2017). However, the routine clinical use of this stratification is challenging as the process of methylation profiling is time consuming and expensive (Shen et al. 2020).

Complete loss of the tri-methylated 27th lysine residue of histone H3 protein, H3K27me3 staining was described by Katz et al (Katz et al. 2018) as a potential tool for differentiating between grade I and II meningiomas, especially in borderline cases. This is clinically relevant as grade I meningioma patients with negative H3K27me3 immunohistochemical staining should be followed up more frequently (and with a lower threshold for intervention in cases of recurrences), because lower expression of the protein is associated with grade II meningiomas, higher recurrence rates and lower overall survival (Katz et al. 2018). These findings have recently been contradicted by Magill et al. who showed that high grade meningiomas have more H3K27 methylation marks compared to grade I meningiomas (Magill et al. 2020). The clinical significance of the latter is as yet unknown but the mechanism underlying H3K27me3 expression in meningiomas has been previously described by Harmanci et al (Harmanci et al. 2017).

SMARCE1 (SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily E, Member 1) expression is highly specific for diagnosing clear cell meningiomas (Tauziède-Espariat et al. 2018), with significantly lower staining intensity observed when compared to other meningioma subtypes. This finding was also confirmed by next-generation sequencing which revealed a loss of function of the SMARCE1 gene in all the clear cell meningiomas tested (Tauziède-Espariat et al. 2018).

Parada et al demonstrated an increased expression of AKAP12 (A-kinase anchor protein 12) in grade I versus II meningiomas via mass-spectrometry and validated these findings via immunohistochemical staining (p=0.032). The authors also showed a significant correlation between low AKAP12 expression and meningioma recurrence, progression and invasion, irrespective of tumour grade (Parada et al. 2018).

ARID4B (AT-rich interactive domain-containing protein 4B) expression has also been described as a discriminating biomarker between grade II and grade I meningiomas with significantly higher immunohistochemical staining in the grade II tumours, though there was no correlation between staining intensity and clinical outcome (Tsai et al. 2017) [insert Table 3].

Discussion

The value of biomarkers in neuro-oncology is becoming increasingly more apparent (Cagney et al. 2018). Most of the neuro-oncology biomarker research to date have focused on the management of gliomas; demonstrated by a brief glioma literature search (using the same keywords and databases described in the methods section above) generating over 9500 articles, compared to the 1779 generated with the meningioma literature search.

This review focused on radiological, immunohistochemical and blood-based biomarkers for differentiating grade II from grade I meningiomas.

Increasing the accuracy of pre/post-treatment (follow-up) radiological grading can play a significant role in disease prognostication and management (Spille et al. 2019, Czyz et al. 2016, Azizyan et al. 2014, Hsu et al. 2010, Hamerla et al. 2019), however, the link between pre-operative MRI findings and post-operative prognosis (irrespective of histological grade) remains controversial (Spille et al. 2019, Azizyan et al. 2014).

The radiological features of a tumour are usually sufficient to make a provisional meningioma diagnosis, but not to make a definite diagnosis or give adequate information with regards prognosis. In an ideal situation, clinicians will have an idea of the likely tumour grade prior to formulating a treatment plan as grade II meningiomas should be treated more aggressively via (Simpson I) resection

with/without adjuvant radiotherapy, compared to the grade I meningiomas (treated with surgery, radiotherapy or a combination of both for Simpson resection grades ≥ 3). Knowledge of the likely tumour grade may also help guide decisions in cases where there is equipoise (due to inaccessible tumour locations, ambiguity of symptoms, meningiomatosis, etc.) surrounding the optimum management plan.

We describe several radiological differences between grade I and II meningiomas. Compared to the grade I tumours, grade II meningiomas usually have a less uniform shape and consistency; are more likely to contain regions of haemorrhage and necrosis; and have a higher cellular density, vascularity and volumetric growth rates. The grade II tumours also have higher Cho/NAA spectroscopy ratios, amide proton transfer signal intensities and significantly higher PET uptakes (FDG and MET). These imaging modalities are already in use in routine clinical practice and can be utilized in meningioma management too [Table 1].

Blood is a non-invasive tissue source that can be easily obtained for biomarker monitoring, with proven roles in the management of other cancers such as prostate, ovarian, pancreatic via the serum biomarkers; prostate-specific antigen (PSA), cancer antigen (CA) 125 and Carbohydrate antigen (CA) 19-9 respectively (Cagney et al. 2018). There is ongoing research into the neuro-oncological use of blood-based biomarkers, with promising results described with circulating tumour cells, exosomes and proteins (Macarthur et al. 2014) (Negroni et al. 2020). In this paper, we reviewed and described the under expression of TIMP-1, TIMP-2 and the over expression of HER2 and Fibulin-2 in grade II compared to grade I meningioma patients.

Cerebrospinal fluid (CSF) is another potential enriched tissue source of neuro-oncological biomarkers (Cagney et al. 2018, Akers et al. 2013), described as superior to blood-based biomarkers when assessing the sensitivity of detectable CSF extracellular vesicles, microRNAs and proteins (Akers et al. 2013, Jia et al. 2017). However, our review did not reveal any CSF markers sensitive enough to differentiate between grade II and I meningiomas.

Histological analysis of tumour samples remains the gold standard for meningioma diagnosis and grading, albeit not always predictive of clinical aggressiveness (Parada et al. 2018). 19.5% – 46% of patients initially diagnosed and managed with a grade I meningioma will represent with a grade II tumour (Champeaux et al. 2019, Corniola et al. 2020). Grade II meningiomas have biological and clinical profiles that are on a spectrum from grade I to III (Marciscano et al. 2016), suggesting that

patients with grade I tumours that progress to grade II may harbour genetic or molecular characteristics that make them more susceptible to the higher grade transformation. We described and reviewed the under-expression of H3K27me3, AKAP12 and the over-expression of ARID4B in grade II meningiomas compared to grade I. SMARCE1 was described to be under-expressed in and highly specific for the clear cell grade II meningioma variant.

CX43 was shown to be differentially expressed between primary (de-novo) and secondary (previously diagnosed as grade I) grade II meningiomas. There was significantly less CX43 staining in the secondary meningiomas compared to the primary cohort (Zhang et al. 2019), suggesting that low levels of Cx43 in benign meningiomas may be a negative prognostic factor for progression to grade II meningiomas

In summary, this review describes an updated selection of clinically relevant biomarkers that may aid in differentiating between grade II and I meningiomas, in predicting the clinically aggressive grade I tumours and thus improving their diagnosis and disease prognostication. These biomarkers may also be helpful in directing treatment as the likely grade I tumours can be managed expectantly (conservatively or radiotherapy) if appropriate, while the grade II tumours may be managed and followed up more aggressively. A high (pre-operative) suspicion of a grade II tumour may also influence surgical strategy as a more aggressive dural excision may be performed (when safe), even in the absence of macroscopic dural invasion. We recommend continued research in this meningioma biomarker field to make further advances in the clinical management of meningioma patients.

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