Invasive meningioma

While most meningiomas are benign and grow slowly, some can become more aggressive and invade surrounding brain tissue, leading to the meningioma classification of these tumors as “invasive.”

Characteristics of Invasive Meningiomas: Tumor Growth and Spread:

Invasive meningiomas have the potential to infiltrate adjacent brain tissue, unlike typical meningiomas, which tend to grow along the meninges and often have well-defined boundaries. They can invade the brain parenchyma, making surgical removal more challenging, as the tumor is not always easily distinguishable from the surrounding brain tissue. Histological Features:

The invasive nature of these tumors is often determined by their histology, which can show cellular atypia, mitotic activity, and sometimes necrosis. These features suggest a more aggressive tumor behavior, which may lead to poorer prognosis and a higher likelihood of recurrence after treatment. Clinical Implications:

Symptoms: Invasive meningiomas can cause neurological symptoms depending on their location and extent of brain involvement. Symptoms may include headaches, seizures, focal neurological deficits (e.g., weakness or sensory loss), or cognitive impairment. Diagnosis: The diagnosis is primarily made using imaging techniques such as magnetic resonance imaging (MRI), where invasive meningiomas may appear as masses that are difficult to differentiate from the surrounding brain tissue. Surgical Challenges: Due to their invasive nature, complete surgical resection can be difficult. In some cases, the tumor's proximity to critical brain structures or its infiltration into brain tissue can make total removal impossible without causing significant neurological damage.

Molecular characteristics of invasive meningioma

The study titled “Differential Expression of Proteins and Genes at the Tumor-Brain Interface in Invasive Meningioma,” published in *Genes Chromosomes Cancer* in November 2024, provides valuable insights into the molecular characteristics of invasive meningiomas, focusing on gene and protein expression at the tumor-brain interface [1)]

The research explores the differential expression of genes in the invasive edge of tumors versus the main tumor body, which has been largely unknown up to now.

Strengths of the Study:

1. **Innovative Approach**: Using the NanoString pan-cancer panel for gene expression analysis is a robust technique that allows for evaluating a large number of genes across different tumor samples. This method enabled the identification of six candidate genes (DTX1, RASGRF1, GRIN1, TNR, IL6, and NR4A1), which are implicated in meningioma invasiveness.

2. **Correlations with Protein Expression**: Immunohistochemistry findings for DTX1 and RASGRF1 corroborated with gene expression results, providing strong evidence of these proteins’ involvement in tumor invasiveness. The inclusion of Ki-67, a well-established marker of cell proliferation, adds depth to the analysis, linking higher expression levels of DTX1 and RASGRF1 to both invasiveness and proliferative activity in the tumor.

3. **Pathway Analysis**: The pathway analysis linking DTX1 and RASGRF1 to key biological processes like cell-cell adhesion and major signaling pathways (Notch, RAS, MAPK, Rho) provides a mechanistic framework to understand how these proteins contribute to brain invasion. These pathways are crucial for cell migration, invasion, and adhesion, which are central to tumor progression.

4. **Clinical Implications**: The findings suggest that DTX1, RASGRF1, and Ki-67 could serve as potential biomarkers for identifying meningiomas with a higher likelihood of brain invasion. This could aid in better prognosis and therapeutic decisions for patients with invasive meningiomas.

Weaknesses and Limitations:

1. **Sample Size**: The study, while informative, involved a relatively small cohort, particularly for the expanded validation of DTX1 and RASGRF1 (21 invasive and 15 noninvasive meningiomas). A larger sample size would strengthen the generalizability of the results and reduce the potential for bias in detecting significant findings.

2. **Inconclusive Results for DTX1**:

The study highlighted a less definitive role for DTX1, especially in meningiomas that were in close contact with the brain but did not show invasion. While increased expression was noted at the invasive edge and in non-invasive tumors with brain contact, further exploration is needed to understand whether DTX1 acts as a universal marker for invasiveness or if its role is more complex.

3. **Mechanistic Insights**:

While the pathway analysis identified important signaling pathways, the study does not delve deeply into the mechanisms by which DTX1 and RASGRF1 modulate brain invasion. Understanding how these proteins interact at the cellular and molecular levels, and whether they directly influence tumor cell behavior, would provide a clearer picture of their role in meningioma pathogenesis.

4. **Lack of Functional Validation**:

The study is based on gene and protein expression profiling, but it lacks functional validation of how the overexpression of DTX1 and RASGRF1 specifically contributes to tumor invasion. Further in vitro or in vivo studies are needed to confirm the causative role of these proteins in meningioma invasiveness.

Conclusion:

This study represents an important step toward understanding the molecular underpinnings of invasive meningiomas and the role of specific genes and proteins in the brain invasion process. The identification of DTX1, RASGRF1, and Ki-67 as potential biomarkers for brain-invasive meningiomas has promising clinical implications, although the small sample size and inconclusive findings regarding DTX1 highlight the need for further research to validate and expand upon these findings. Future studies with larger cohorts and functional assays will be essential to fully elucidate the role of these proteins in meningioma invasion and progression.

Treatment and Prognosis

Surgical Resection: Surgery remains the primary treatment for meningiomas. However, achieving complete resection can be challenging in invasive cases, particularly when the tumor has infiltrated

nearby brain structures. Radiotherapy: In cases where complete surgical resection is not possible, radiation therapy may be used to control tumor growth and prevent recurrence. Stereotactic radiosurgery can be an effective option for small, well-defined tumors. Chemotherapy and Targeted Therapy: These options are generally less effective for meningiomas, but there is ongoing research into molecularly targeted therapies, particularly for more aggressive, invasive forms of the disease. Drugs targeting specific pathways, like those involving the RAS or MAPK pathways, may hold promise for future treatment strategies.

Prognosis

The prognosis for invasive meningiomas is generally worse than for non-invasive types due to their potential for recurrence and difficulty in complete removal. Recurrence rates can be high, particularly if the tumor has deeply invaded brain tissue. Patients with invasive meningiomas often require close follow-up, including regular imaging, to monitor for recurrence or progression.

Invasive intracranial meningioma is a common neoplasm of central nervous system, which can infiltrate adjacent tissues (dura mater, arachnoid membrane, vascular space and skull) without atypical hyperplasia [2) 3)]

In general, the pathological nature of meningioma determines its association with the brain parenchyma, which is that benign meningioma is usually compressive to the brain parenchyma due to its expansive growth, and malignant meningioma is invasive into the neighboring brain parenchyma due to its intrusive growth [4) 5)]. However, clinical observations have indicated that there is a sub-group of benign meningioma displaying a malignant growth pattern, that is, invasion into the neighboring brain tissue [6) 7) 8) 9) 10)].

According to the experience gained in 19 cases, it was observed that there were certain features shared by these invasive benign meningiomas. The peak age of onset was ~50 years; the main manifestation was mild focal neurological deficits, which included dysphasia, and decreased sensation and muscle power of the contralateral limb. The MRI findings usually had the following characteristics: The lesions were located at the convexity of the cerebral hemisphere involving the central lobe, with an extensive base at the dural matter and evident ‘tail sign’; there was a minimal boundary between the tumor and the neighboring brain cortex; finally, and probably most importantly, the apex of tumor often enwrapped the normal brain tissue and associated vessels.

Due to the malignant growth, it was challenging to completely remove this benign meningioma while ensuring that neurological function remained intact. Resection of the earliest 4 cases was performed according to the traditional extra-capsular strategy, which was to coagulate and divide the tumor base first, and then continue the dissection along the interface between the tumor and brain parenchyma. This approach inevitably damaged the vessels transiting from and into the tumor. The observation that all 4 cases had permanent neurological deficits confirmed the disadvantage associated with this surgical strategy. Following careful analysis of the surgical outcomes, the resection method was modified by combining intra- and extra-capsular approaches. The first step was the same as the classical method, which was to coagulate and divide the tumor base. Afterwards, intra-capsular extirpation of the central part of the tumor was performed. Care was taken not to damage the transit vessels when approaching the tumor-brain interface. The enucleation of the central part of the tumor created a working space, which greatly facilitated the identification of the

transit vessels. After this, the tumor was separated from brain parenchyma along the sub-arachnoid membrane. The use of a sponge during this dissection process was important. Finally, it was critical to separate the enwrapped brain cortex and associated vessels from the invading 'cauliflower-like' nodules of the meningioma. It is recommended that no efforts are spared in this process, since the enwrapped brain tissue may have retained its ability to function. The observation that there was only 1 case with mild neurological impairment post-operatively in the later 15 cases confirms the advantage of the modified strategy.

In summary, the present study further revealed the clinical features of the invasive benign meningioma and indicated the advantage of combined intra-extra capsular strategy for the surgical resection [11].

Identification of risk factors for perioperative epilepsy remains crucial in the care of patients with meningioma. Moreover, associations of brain invasion with clinical and radiological variables have been largely unexplored. Brain invasion was identified as a new and strong predictor for preoperative, but not postoperative, seizures. Although also associated with increased peritumoral edema, seizures in patients with invasive meningioma might be facilitated substantially by cortical invasion itself. Consideration of seizures in consultations between the neurosurgeon and neuropathologist can improve the microscopic detection of brain invasion [12].

Case series

2018

Hess et al., hypothesized that invasion of the cortex and subsequent increased edema facilitate seizures, and they compared radiological data and perioperative seizures in patients with brain-invasive meningioma or noninvasive meningioma.

Correlations of brain invasion with tumor and edema volumes and preoperative and postoperative seizures were analyzed in univariate and multivariate analyses.

Totals of 108 (61%) females and 68 (39%) males with a median age of 60 years and harboring totals of 92 (52%) grade I, 79 (45%) grade II, and 5 (3%) grade III tumors were included. Brain invasion was found in 38 (22%) patients and was absent in 138 (78%) patients. The tumors were located at the convexity in 72 (41%) patients, at the falx cerebri in 26 (15%), at the skull base in 69 (39%), in the posterior fossa in 7 (4%), and in the ventricle in 2 (1%); the median tumor and edema volumes were 13.73 cm3 (range 0.81-162.22 cm3) and 1.38 cm3 (range 0.00-355.80 cm3), respectively. As expected, edema volume increased with rising tumor volume ($p < 0.001$). Brain invasion was independent of tumor volume ($p = 0.176$) but strongly correlated with edema volume ($p < 0.001$). The mean edema volume in noninvasive tumors was 33.0 cm3, but in invasive tumors, it was 130.7 cm3 ($p = 0.008$). The frequency of preoperative seizures was independent of the patients' age, sex, and tumor location; however, the frequency was 32% ($n = 12$) in patients with invasive meningioma and 15% ($n = 21$) in those with noninvasive meningioma ($p = 0.033$). In contrast, the probability of detecting brain invasion microscopically was increased more than 2-fold in patients with a history of preoperative seizures (OR 2.57, 95% CI 1.13-5.88; $p = 0.025$). In univariate analyses, the rate of preoperative seizures correlated slightly with tumor volume ($p = 0.049$) but strongly with edema volume ($p = 0.014$), whereas seizure semiology was found to be independent of brain invasion ($p =$

0.211). In multivariate analyses adjusted for age, sex, tumor location, tumor and edema volumes, and WHO grade, rising tumor volume (OR 1.02, 95% CI 1.00-1.03; p = 0.042) and especially brain invasion (OR 5.26, 95% CI 1.52-18.15; p = 0.009) were identified as independent predictors of preoperative seizures. Nine (5%) patients developed new seizures within a median follow-up time of 15 months after surgery. Development of postoperative epilepsy was independent of all clinical variables, including Simpson grade (p = 0.133), tumor location (p = 0.936), brain invasion (p = 0.408), and preoperative edema volume (p = 0.081), but was correlated with increasing preoperative tumor volume (p = 0.004). Postoperative seizure-free rates were similar among patients with invasive and those with noninvasive meningioma (p = 0.372).

Brain invasion was identified as a new and strong predictor for preoperative, but not postoperative, seizures. Although also associated with increased peritumoral edema, seizures in patients with invasive meningioma might be facilitated substantially by cortical invasion itself. Consideration of seizures in consultations between the neurosurgeon and neuropathologist can improve the microscopic detection of brain invasion [13].

2017

From February 2014 to February 2016, 59 patients with invasive meningioma were enrolled in a study. Invasive meningioma was confirmed in all patients by operation. Information about clinical manifestations, pathological features, preoperative imaging and surgical treatment were collected and analyzed. After surgery, pathological specimens were collected, and cases were confirmed as invasive meningioma by pathological examination. The course of disease ranged from 15 days to 7 years (average, 13.2 months). We used World Health Organization (WHO) criteria for classification of meningioma in the nervous system tumors as our reference. Symptoms were as follows: Intracranial hypertension (29 cases), cranial nerve dysfunction (10 cases), epilepsy (11 cases) and other symptoms (9 cases). We had 56 cases of WHO grade I; 6 cases of WHO grade II and 7 cases of WHO grade III. Surgical removal was: Simpson grade I (56 cases), Simpson grade II (2 cases), Simpson grade III and above (56 cases). We used before surgery imaging data to formulate our surgical plan. In general, during surgeries we did not proceed to complete resection, because in the majority of cases, some key structures were invaded and meningioma was very deep and any attempt for total resection could easily lead to significant damage to these structures [14].

1995

A study was undertaken to investigate the correlation between histological invasiveness and proliferating potential and clinical recurrence in meningioma. In 39 meningiomas, the histological findings at the tumour-brain interface zone were classified into 3 types, consisting of 29 cases of non-invasion (NON). 7 cases of nodular invasion (NOD), and 3 cases of intermingled invasion (INT). Proliferating cell nuclear antigen (PCNA) and argyrophilic nucleolar organizer region (AgNOR) indices were studied. PCNA indices (mean +/- standard error) of NON, NOD. and INT were 1.7 +/- 0.1%, 5.2 +/- 0.5%, and 7.5 +/- 0.7%. respectively, and the AgNOR indices (dot number/nucleus) were 1.50 +/- 0.03, 2.00 +/- 0.04, and 2.22 +/- 0.07, respectively. Significant differences were found among the three types in both parameters. Clinically, tumour recurrence was observed in 1/29 NON, 4/7 NOD, and 2/2 INT cases, indicating a higher incidence of recurrence in invasive meningiomas (NOD plus INT). Four of 32 patients who underwent gross total removal of the tumours showed recurrence, and all of these four tumours were invasive meningiomas. The results of the present study showed that tumour invasiveness as measured by PCNA + AgNOR indices correlated well with high proliferative

potential and clinical recurrence [15].

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