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Towards Molecular Classification of Meningioma: Evolving Treatment and Diagnostic Paradigms

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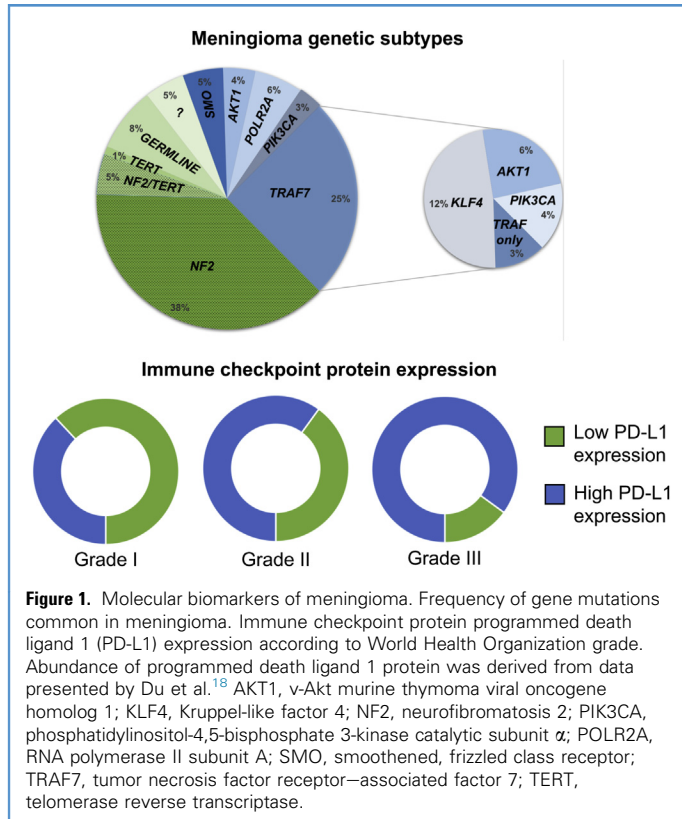[E-mail: garnette@ucalgary.ca]

Meningioma, a common primary brain tumor in adults, is graded based on World Health Organization criteria that rely on histology alone. This approach is unable to determine conclusively which tumors, especially benign or atypical, will recur. Molecular characterization of meningioma has identified genetic biomarkers that can predict tumor behavior. Only a few genetic changes are known to classify >85% of all meningioma and clinical trials using targeted therapy to genetic subtypes of meningioma are under way. Immunotherapy is also being trialed in treating high-grade and recurrent meningioma. This review summarizes recent developments characterizing meningioma using genetic and immunologic biomarkers and how these molecular tools may be integrated into existing care together with current World Health Organization grading to improve diagnosis, prognosis, and therapy.

CURRENT MENINGIOMA DIAGNOSIS AND CONTROVERSIES

Meningioma, a common primary intracranial tumor, accounts for approximately 36% of all adult brain tumors, with an incidence of approximately 98/100,000 people.[1-3]

According to World Health Organization (WHO) guidelines, approximately 80% of meningioma is classified as grade I or benign, 10%—18% as grade II or atypical, and approximately 2%—4% as grade III or malignant.[4,5] Although grade I meningioma has a low 5-year recurrence rate after surgery, approximately 30% invariably recurs over the patient's lifetime.[6] In contrast, the 5-year recurrence in atypical and anaplastic meningioma can be as high as 50% and 80%, respectively.[7] Based on WHO criteria that rely on histology alone, it is not possible to determine which tumors, especially benign or atypical, will recur. Furthermore, both meningioma grades I and II may progress to grade III but it is unclear which cases undergo malignant transformation.[3]

WHO grading is determined by scoring for several histomorphologic markers. Meningioma has a heterogenous morphology and 15 subtypes are included in WHO criteria.[5] Nine variants make up grade I tumors, and grades II and III each consist of 3 variants. Grade I meningioma is most commonly meningothelial, fibrous, or a combination of these 2 subtypes (transitional). Grade II tumors are characterized either by having a mitotic count of 4—19 events per 10 high power fields together with evidence of brain invasion or by having >4 mitotic events and showing ≥3 of 5 morphologic criteria,

including 1) high cellularity, 2) small cells (clusters of cells with high nuclear/cytoplasmic ratio), 3) sheeting (loss of whorling or fascicular architecture), 4) spontaneous necrosis, and 5) prominent nucleoli.[5] Meningioma with clear cell or chordoid morphology is also grade II.[8,9] Grade III meningioma is classified based on >20 mitotic events per 10 high power fields, showing loss of cellular architecture that resembles meningioma (i.e., sarcomatous or carcinomatous) and also showing brain invasion and necrosis.[5] Grade III tumors may also be classified when rhabdoid cells or papillary features are present.[5]

This complex classification system is one that is subject to a moderate degree of interobserver variation. Discordance is particularly common in borderline cases.[10] The recent NRG Oncology RTOG (Radiation Therapy Oncology Group) Trial 0539 showed that discordance in the reported number of mitotic events is approximately 20%.[10] Discordance was even higher when reporting on levels of hypercellularity (26.7%), sheeting (25.6%), and macronucleoli (23.3%). Subsequently, it is standard practice for many clinics to conduct WHO grading by 2 independent neuropathologists. Moreover, the prognostic value of certain histologic markers used in the characterization of meningioma has come into question in

Figure 1. Molecular biomarkers of meningioma. Frequency of gene mutations common in meningioma. Immune checkpoint protein programmed death ligand 1 (PD-L1) expression according to World Health Organization grade. Abundance of programmed death ligand 1 protein was derived from data presented by Du et al.[18] AKT1, v-Akt murine thymoma viral oncogene homolog 1; KLF4, Kruppel-like factor 4; NF2, neurofibromatosis 2; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; POLR2A, RNA polymerase II subunit A; SMO, smoothened, frizzled class receptor; TRAF7, tumor necrosis factor receptor—associated factor 7; TERT, telomerase reverse transcriptase.

recent years. For example, histologically benign meningioma with a component of brain invasion is classified as grade II, yet studies have shown poor correlation between brain invasion and tumor recurrence or progression.[11]

CURRENT TREATMENT AND IMAGING SURVEILLANCE GUIDELINES

There are no established screening guidelines for meningioma. Although treatment paradigms are fairly standardized across the world, quality evidence is lacking. Current clinical practice is largely based on institutional experience and facilities available therein, long-standing traditional procedures, and experience-based practice. The treatment modalities include observation using serial surveillance neuroimaging (computed tomography/magnetic resonance imaging), surgery, stereotactic radiosurgery (SRS), fractionated radiotherapy (FRT), experimental chemotherapy, or radionuclide therapy. Management is heavily based on clinical profile, WHO grade, and extent of

resection, which is beginning to seem suboptimal with increasing understanding of tumor biology.

Therapy for patients with meningioma is highly individualized. Most asymptomatic or incidentally detected meningioma may be managed by observation with serial surveillance neuroimaging.[12] However, there is no class I or II evidence to support this convention. The indications for surgery are mass effect, symptoms corroborating with the location of the tumor, and patient's preference. Recent advancements in microneurosurgery, cortical mapping, and image-guided surgery have contributed enormously to the safety of surgical resection. However, some investigators have reported on undesirable long-term sequelae in patients who have undergone surgical resection. Van der Vossen et al.[13] in a recent cross-sectional study, analyzed the neuropsychological profile of such patients. These investigators reported that 23% experienced cognitive complaints, 29% showed anxiety, and 23% showed depressive symptoms on long-term follow-up. However, preexisting cognitive

deficits significantly improve after surgical intervention.[14] A careful assessment of risk versus benefit ratio should be performed before embarking on surgical intervention. The main goal of surgery is the complete resection of meningioma, including the dural attachment and infiltrated bone. Whenever possible, a Simpson grade 0 excision (excision of dural margin of 2—4 cm) is attempted to mitigate the chance of recurrence. However, this is not feasible in skull base lesions, in which Simpson grade II excision (complete resection with coagulation of dural attachment) is considered optimal.

Although surgical excision continues to be the mainstay of management of meningioma, alternative therapeutic measures such as SRS or FRT are considered when the patient is in poor clinical condition, serving as a contraindication to surgery, or when the lesion is inoperable. Generally, for grade I and II meningioma, a gross total resection would suffice. Subtotal or partial resections are combined with SRS or FRT. FRT may be considered even after complete resection of grade II meningioma. For grade III meningioma, adjuvant therapy such as SRS, FRT, chemotherapy, or radionuclide therapy is usually considered after surgical resection.[15] After gross total resection, 12% and 19% of all tumors, including grade I, recur within the first and second decade, respectively.[16,17] This situation is presumably because of unfavorable genetics or molecular biology, which in turn potentially instigates tumor recurrence.

GENETIC CHARACTERIZATION OF MENINGIOMA

Molecular characterization of meningioma has identified genetic biomarkers that can predict prognosis and tumor behavior. Only a few genetic changes classify >85% of all meningioma (**Figure 1**). This review also outlines propositions on how specific molecular biomarkers might be incorporated into the clinical management of patients with meningioma (summarized in **Table 1**). We also describe the most common and clinically relevant genetic mutations of meningioma that have an influence on tumor characteristics such as tumor behavior, malignancy, and location (summarized in **Table 2**) and list targeted