Benign Intracranial Tumors

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KEYWORDS

• Benign intracranial tumors • Meningioma • Schwannoma • Neurofibromatosis
• Schwannomatosis

KEY POINTS

- Meningiomas and schwannomas account for almost all incident benign intracranial tumors.
- Risk factors for meningiomas and schwannomas include exposure to ionizing radiation, as well as various genetic diseases and gene mutations.
- Although most benign intracranial tumors are primarily treated with surgery or radiation, ongoing research has identified an increasing number of effective or promising systemic therapies.

INTRODUCTION

Although there are many types of histologically benign primary intracranial tumors, the incidence of meningiomas and schwannomas in the general population accounts for the almost all such benign tumors. Although surgery is often curative for benign tumors, meningiomas and schwannomas are variably associated with unique challenges that limit the curability of individual tumors. Among these, 3 primary considerations include anatomically limited surgical accessibility of certain tumors; risk of recurrence, which is especially high after incomplete resection; and the relatively ineffective nature of traditional types of chemotherapy. Epidemiologic and genetic information for both meningiomas and schwannomas are presented, as well as therapeutic advances and considerations.

MENINGIOMA

Key Points

- Meningiomas are the most common primary intracranial tumor in adults.
- More than 80% of incident meningiomas are World Health Organization (WHO) grade I (benign meningiomas).

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- Most meningiomas occur sporadically, though risk is increased with exposure to ionizing radiation and with germline mutations in the *NF2*, *SMARCB1*, *LZTR1*, or *SMARCE1* genes.

Epidemiology

Meningiomas are the most common primary intracranial tumor in adults, accounting for more than one-third of all primary central nervous system tumors.[1] The annual incidence of meningiomas is 8.3 per 100,000 population[1] and generally increases with age. Patients older than 70 years of age have a 3.5-fold increased risk of meningioma development compared with those younger than 70 years old.[2] The incidence rate in women is 56% higher than in men.[1]

Although almost all meningiomas occur sporadically (eg, without an identifiable risk factor) and as a single tumor, the risk of single or multiple such tumors is increased with exposure to ionizing radiation.[3,4] Among childhood cancer survivors, the average risk of meningioma development is increased nearly 10-fold by exposure to radiation for cancer treatment, and the median time to meningioma diagnosis in this cohort is 17 years.[3] In another systematic review of cases of radiation-associated meningiomas, the average time from radiation to meningioma development was 22.9 years, and 11.9% of reported cases had multiple meningiomas, with greater risk among patients who received higher doses of radiation.[5] Among those reported cases, 68% of radiation-induced meningiomas were WHO grade I, 27% were WHO grade II, and 5% were WHO grade III.[5]

Correlations have also been shown between meningioma development and prior head trauma or various viral infections (eg, adenovirus), although reports for these are inconsistent and the true association with tumor risk remains unknown.[6–8] Finally, excessive hormone exposure has been correlated with meningioma development and, in fact, progesterone receptors are expressed on more than 70% of meningiomas, and estrogen receptors on nearly 30%.[8,9] However, whether hormones are drivers of tumor development remains unknown.

In addition to extrinsic risk factors, 2 genetic diseases are associated with a high rate of meningioma development. Neurofibromatosis 2 (NF2) is an autosomal dominant tumor predisposition syndrome associated with loss of function mutations in the *NF2* gene on chromosome 22, leading to cell growth signaling dysregulation and constitutive activation of various pathways, including mammalian target of rapamycin complex (mTORC)-1 and mTORC2 signaling.[10,11] Although the hallmark of NF2 is bilateral vestibular schwannomas, up to 80% of patients also develop 1 or more meningiomas by the age of 70 years.[12–14] In fact, meningiomas are often the symptomatic tumor in children diagnosed with NF2, whereas adults are more commonly diagnosed after developing symptoms of vestibular schwannomas.[15]

Schwannomatosis, a separate autosomal dominant tumor predisposition syndrome, is associated with multiple schwannomas, which are usually not on the vestibular nerve (although unilateral vestibular schwannomas have been described).[16–19] Additionally, about 5% of patients with schwannomatosis will develop 1 or more meningiomas.[20] Although schwannomatosis is inherited in an autosomal dominant pattern, the disease arises from multiple genetic loci and up to 85% of cases are nonfamilial.[20] SWItch/Sucrose NonFermentable (SWI/SNF)-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (*SMARCB1*), a gene encoding part of a nucleosome remodeling complex, is on chromosome 22q11 adjacent to the *NF2* gene, and mutations therein are responsible for 40% to 50% of familial schwannomatosis cases and about 10% of sporadic cases.[21,22] Germline mutations in Leucine Zipper-Like Transcription Regulator 1 (*LZTR1*), also located on chromosome 22q11,