INTRODUCTION — Most meningiomas are benign, but their location in the central nervous system can cause serious morbidity and/or mortality.

The epidemiology, risk factors, and pathologic classification of meningiomas will be reviewed here. Other topics on meningioma include:

- Clinical presentation and diagnosis of meningioma (see "Meningioma: Clinical presentation and diagnosis")
- Treatment of benign (WHO grade I) meningioma (see "Treatment of benign (WHO grade I) meningioma")
- Treatment of atypical (WHO grade II) and malignant (WHO grade III) meningioma (see "Atypical and malignant meningiomas")
- Systemic treatment of recurrent meningioma (see "Systemic treatment of recurrent meningioma")

EPIDEMIOLOGY — Meningiomas account for about one-third of all primary brain and central nervous system tumors (table 1 and figure 1) [1,2]. (See "Incidence of primary brain tumors").

According to the Central Brain Tumor Registry in the United States (CBTRUS), there were approximately 18,000 new cases of meningioma diagnosed annually from 2004 to 2006. Currently, the estimated prevalence in the United States is that there are 170,000 people with meningioma, because of the prolonged natural history of meningiomas and because asymptomatic elderly patients and those with significant comorbidity are often managed without active intervention.

The incidence of meningioma increases progressively with age, with most cases occurring in older individuals. Meningiomas are rare in children [3], except in those with hereditary syndromes such as neurofibromatosis type 2 (NF-2) or antecedent therapeutic radiation therapy [4,5]. (See 'Ionizing radiation' below and 'Genetic factors' below.)

Overall, meningiomas are more common in women, with a female to male ratio of about two or three to one [4,6,7]. For spinal meningiomas, which comprise about 10 percent of all meningiomas, the female to male ratio is even higher, approximately nine to one. This female predominance is less pronounced or absent in those with atypical or anaplastic meningiomas, children, and those with radiation-induced meningiomas.

Older studies estimated that more than 90 percent of meningiomas were WHO grade I, approximately 5 percent were grade II, and 1 to 3 percent were grade III [6]. However, contemporary studies have found that the incidence of grade II lesions of 20 to 35 percent based upon application of the 2000 and
2007 World Health Organization classification system [8,9]. Grade III meningiomas remain rare. (See \textit{Pathology} below.)

\textbf{RISK FACTORS} — A number of factors have been studied for a possible relationship to the development of meningiomas and other brain tumors. The factors most intensively investigated as having a potential etiologic role in meningioma are discussed here. Factors associated with other types of brain tumors are reviewed separately. (See \textit{"Risk factors for brain tumors"}.)

\textbf{Ionizing radiation} — Multiple lines of evidence have linked exposure to ionizing radiation and the subsequent development of meningiomas after both low-dose and high-dose irradiation [7,10]. Radiation-induced meningiomas have a higher incidence of multiplicity and atypia compared to sporadic meningiomas. An increased risk of meningioma following a lengthy latency period has been established in a variety of situations.

The most important implication of this relationship is for patients who received radiation therapy for the treatment of malignancy.

\textbf{Radiation therapy for malignancy} — Radiation is frequently used therapeutically, and thus results in exposure of the central nervous system either as a direct consequence of treatment or by incidental exposure. Clinical situations where this is particularly important include the radiation therapy (RT) for primary malignancies of the central nervous system (CNS) or the head and neck region, as well as prophylactic craniospinal irradiation to prevent CNS relapse as a component of treatment for acute leukemia or other malignancy. (See \textit{"Complications of cranial irradiation", section on 'Radiation-induced tumors'} and \textit{"Complications of cranial stereotactic radiosurgery", section on 'Second tumors after SRS'}.)

Although the absolute risk associated with RT is not known, the latency period is more than 20 years in many cases. Long-term follow-up of epidemiologic studies has observed that the incidence continues to rise even after several decades.

The potential clinical implications of the relationship between meningioma and therapeutic radiation are illustrated by several studies:

- In the Childhood Cancer Survivor Study of over 14,300 patients who survived at least five years after their initial diagnosis of cancer, meningiomas have developed in 170 patients (1.2 percent) [11]. Patients had been variably treated with surgery, chemotherapy, radiation, or a combined modality approach. In the most recent report from this study, the median time to diagnosis of meningioma was 23 years and the incidence appeared to be rising for at least 30 years after the original diagnosis. The association with meningioma was specifically linked to antecedent radiation rather than other forms of treatment, and the risk was directly related to the dose of cranial irradiation. A similar increased risk of meningioma was observed in the British Childhood Cancer Survivor Study [12].

- The risk of developing a meningioma appears to be highest for those treated at a young age. Furthermore, the incidence may be substantially higher if asymptomatic individuals are systematically screened with imaging techniques. In a study of 49 childhood survivors of leukemia who were evaluated using MRI, treatment with craniospinal irradiation between the ages of one and eight years was associated with the development of meningioma in 11 (22 percent) at a mean latency period of 25 years [5]. Three of the 11 cases had multiple meningiomas. There was no evidence of a plateau in the development of meningioma, and the incidence may have been even higher in those studied more than 20 years after the original diagnosis. Additional study is required to determine whether MRI screening should be used routinely in patients who received craniospinal irradiation in childhood.
Incidental radiation exposure — An association between radiation and the subsequent development of meningioma has been observed in a number of other clinical settings:

- **Tinea capitis** – Until the 1950s, low doses of irradiation were used to treat tinea capitis. Epidemiologic studies on these patients provided the first evidence of the causal relationship between radiation and the subsequent development of meningioma.

  An analysis of over 11,000 children treated for tinea capitis found a sevenfold increase in the incidence of meningioma [13]. The mean latency period was 36 years, but latency was shorter in those who received higher doses of radiation [7]. Multiple meningiomas were more common in patients who had received radiation than in those with sporadic tumors. In addition, recurrence rates were higher in those with radiation-induced meningiomas.

- **Medical imaging** – Dental x-rays cause a much lower level of radiation exposure to the brain compared to that used in treating tinea capitis. However, several studies have reported an increased risk of meningioma associated with frequent dental x-rays [14-18]. In a population-based case-control study of over 2500 patients, meningioma cases were twice as likely as controls to report ever having had a bitewing dental x-ray [18]. Patients who reported having at least one panorex film before the age of ten had a 4.9 times increased risk of meningioma (95% CI, 1.8-13.2). Across multiple studies, the reported risk has been highest for multiple x-ray examinations and childhood exposure, primarily in an era when the dose of dental x-rays was higher than with current technology [14,17-19]. It is also important to recognize that recall bias can influence associations found in case-control studies such as these, and validation of dental records was not performed in most of these studies [20].

  Childhood exposure to diagnostic head CTs may also be associated with an increased risk of brain tumors, including meningiomas [21,22]. (See "Radiation-related risks of imaging studies", section on 'Pediatrics'.)

- **Atomic bomb exposure** – An increased incidence of meningiomas has been observed in survivors of the atomic explosions in Japan [23,24]. The increased incidence of meningioma was more pronounced in those who received higher radiation doses and those who were younger at the time of exposure [25].

Genetic factors

- **Neurofibromatosis type 2** — Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder predisposing to multiple neoplastic lesions. This disorder is due to a mutation in the NF2 gene, a tumor suppressor gene on chromosome 22 which encodes a membrane cytoskeletal protein called merlin or schwannomin [26] that appears to be involved in actin-cytoskeleton organization [27]. Other modifier genes may also be involved [28]. (See "Neurofibromatosis type 2", section on 'Molecular pathogenesis'.)

  Approximately one-half of individuals with NF2 have meningiomas, and multiple meningiomas are often present [29]. Most meningiomas are intracranial, although intradural, extramedullary spinal meningiomas are also seen. (See "Neurofibromatosis type 2", section on 'Meningiomas'.)

  The incidence increases with age, and lifetime risk of developing a meningioma may be as high as 75 percent [30]. Patients with NF2 tend to develop meningiomas at an earlier age than those with sporadic meningiomas. The meningiomas seen in patients with NF2 are more frequently atypical or anaplastic compared with sporadic tumors [31,32].

  In addition, many sporadic meningiomas are associated with mutations in or inactivation of merlin [33-35]. Evaluation of these mutations in sporadic meningiomas has corroborated the hypothesis that the formation of aggressive meningiomas follows a multistep tumor progression model [36].
Other hereditary syndromes — Familial meningioma distinct from neurofibromatosis type 2 is a rare disorder with less than 20 families described in the literature. Since the NF II gene is not deleted in these tumors [37], there must be a second tumor suppressor gene locus contributing to meningioma development.

Hormonal factors — A number of lines of evidence suggest that hormonal factors have a role in the development of meningioma [1]:

- A higher incidence of meningioma in post-pubertal women compared with men.
- The female: male ratio is highest during the peak reproductive years and decreases in elderly individuals.
- Progesterone and androgen receptors are present in approximately two-thirds of patients, while estrogen receptors have been identified in approximately 10 percent of cases [38-40].

The possible relationship between either hormone replacement therapy or oral contraceptive use and the risk of meningioma has been evaluated in several studies [1,41-46]. These studies have yielded conflicting results about the role of exogenous hormones, and no definitive conclusions can be drawn. Some but not all of these studies have also suggested a protective effect of smoking and an increased risk with higher body mass index (BMI), both of which could potentially be mediated through their effects on endogenous estrogen levels [41,44-46].

The possible relationship between meningiomas and hormonal factors has led to the evaluation of treatment with systemic oral progestational agents and other hormonal treatments in patients with recurrent meningioma not amenable to surgery and/or radiation therapy. However, inhibition of these receptors has not been demonstrated to alter the natural history of recurrent meningiomas. (See "Systemic treatment of recurrent meningioma", section on 'Hormonal therapy'.)

Breast cancer — A moderately increased risk of meningioma has been reported in women with breast cancer, and a similar increase in the incidence of breast cancer has been observed in women with a history of meningioma [1,47]. Whether this relationship is due to shared hormonal risk factors, other risk factors causing both diseases, or an underlying genetic predisposition is unclear [1].

Head trauma — Head trauma was originally suggested as a cause of meningioma in 1922 [48], and a number of subsequent studies have analyzed the role of head trauma as an etiologic factor for brain tumors, with conflicting results [19,49-51]. Improved recall in patients with meningioma may have contributed to a detection bias in some of these studies.

The possible etiologic relationship with trauma is illustrated by two large studies:

- A cohort of over 228,000 individuals from Denmark who had been hospitalized for skull fracture, concussion, or other head trauma was analyzed for the risk of subsequently developing meningioma [50]. Although the risk of meningioma was increased after a median follow-up of eight years, the difference was not statistically significant (standardized incidence ratio 1.2, 95% CI 0.8-1.7).

- An international, case-control study investigated the role of head trauma as a cause of brain tumors and included 330 patients with meningioma [49]. There was an increased risk of meningioma among men with head injuries at least five years before the diagnosis of meningioma (odds ratio [OR] = 1.5). The risk was more pronounced for those whose injury occurred 15 to 24 years prior to diagnosis (OR = 5.4).

Cell phone use — Multiple studies have looked at a possible link between cell phone usage and the subsequent development of brain tumors. At present, there is no conclusive evidence supporting a causal relationship. However, the prolonged latency period seen with ionizing radiation suggests that...
longer follow-up is required [1]. (See "Risk factors for brain tumors", section on 'Cellular telephones and radiofrequency radiation'.)

PATHOLOGY

WHO classification — Meningiomas are classified according to the World Health Organization (WHO) schema, which is based upon morphologic criteria [52]. The 2000 and 2007 versions of the WHO classification system divides meningiomas into three groups (table 2):

- **WHO grade I** — Benign meningiomas (WHO grade I) (picture 1) are subdivided into a number of subtypes (table 2). WHO grade I meningiomas do not meet any of the criteria for a higher grade lesion based upon morphologic criteria. The treatment approach is the same for all of the subtypes of benign meningiomas.

- **WHO grade II** — WHO grade II meningiomas have increased mitotic activity (≥4 mitoses per ten high powered fields) and three or more of the following features: increased cellularity, small cells with a high nuclear:cytoplasmic ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, or foci of spontaneous or geographic necrosis (picture 1). Chordoid, clear cell, and atypical meningiomas are classified as WHO grade II.

- **WHO grade III** — WHO grade III meningiomas have ≥20 mitoses per ten high powered fields and/or malignant characteristics resembling carcinoma, sarcoma, or melanoma. Features that support the diagnosis of malignant meningioma include the loss of usual meningioma growth patterns, infiltration of underlying brain, abundant mitoses with atypical forms, and multifocal microscopic foci of necrosis (picture 1). Papillary, rhabdoid, and anaplastic meningiomas are classified as WHO grade III.

The WHO 2000 grading system represented a significant change from the 1993 version, with more objective and reproducible definitions of grade II and grade III lesions [1]. This has resulted in a substantial shift with increasing numbers of patients with WHO grade II tumors. In two large studies that utilized the WHO criteria published in 2000, the incidence of grade II meningiomas increased from 5 to 7 percent prior to 2000 to 20 to 38 percent [8,53].

In addition to increasing the percentage of patients with atypical meningiomas, the refined WHO criteria appear to be more accurate prognostically. A study in patients with atypical or malignant meningiomas compared the 2000/2007 classification system with the 1993 system [54]. Using the revised system, the differences in progression-free survival between histologic groups were statistically significant whereas they were not based upon the older schema.

The major difference between the 2007 and 2000 WHO versions is that brain invasion is now a criterion for classifying a meningioma as grade II or grade III in a lesion that would otherwise be considered grade I.

**Impact of grade on prognosis** — The WHO grading system correlates with outcome and thus has a major impact on treatment planning.

Patients with WHO grade II or grade III meningiomas are significantly more likely to have invasive disease, a local recurrence following the initial treatment, and ultimately to have a shorter overall survival compared to patients with a WHO grade I meningioma. Overall reported rates of recurrence for patients with grade I, II, and III meningiomas are 7 to 25, 29 to 52, and 50 to 94 percent in various series [52,55-58].

The progressive worsening of prognosis with WHO grade III (anaplastic) meningiomas compared to grade II (atypical) meningiomas is illustrated in by a single-institution series of 1098 patients who were treated surgically between 1986 and 2004 [55]. In this series, 74 cases (7 percent) were classified as either atypical (40 cases) or anaplastic (24 cases); the mean follow-up was over five years. The five-
year recurrence-free survival rate was significantly better for grade II compared with grade III meningiomas (87 versus 29 percent).

**Pathogenesis** — Meningiomas are thought to arise from a multistep progression of genetic changes. These alterations may involve activation of oncogenes or inactivation of tumor suppressor genes. It is likely that the total accumulation of genetic changes rather than the sequence in which they are acquired is important in neoplastic transformation.

The two genes that have been most frequently implicated in the pathogenesis of meningioma are NF2 and DAL-1.

- **Neurofibromatosis type 2** — Patients with neurofibromatosis type 2 have an increased incidence of meningioma, which is associated with germline mutations in the NF2 gene on chromosome 22 [59,60]. Mutations of the NF2 gene have also been identified in approximately one-half of patients with sporadic meningioma. (See "Neurofibromatosis type 2".)

  The product of the NF2 gene is a membrane cytoskeletal protein called merlin, which is also known as schwannomin. Merlin is thought to act as a tumor suppressor gene, the absence of which promotes cell growth.

- **DAL-1** — Another tumor suppression gene, DAL1, and its gene product, protein 4.1B, are believed to be frequently involved in the initiation of meningiomas that do not contain mutations in the NF2 gene. DAL1 loss has been demonstrated in approximately 60 percent of sporadic meningiomas [61].

NF2 gene abnormalities generally can be identified in patients with atypical (WHO grade II) or malignant (WHO grade III) meningioma. Additional, more complex genetic changes are also frequently present, consistent with the progression of these tumors [62,63].

**SUMMARY**

- Meningiomas account for approximately one-third of primary central nervous system tumors, occurring primarily in older individuals with a female predominance (table 1 and figure 1). (See 'Epidemiology' above.)

- The etiology of meningioma is not known in most cases. However, there is a clear association with antecedent radiation exposure, which is associated with a latency period that may exceed 30 years. Meningiomas are a frequent manifestation of neurofibromatosis type 2 (NF2), and somatic mutations in the NF2 may also contribute to the development of sporadic meningiomas. (See 'Risk factors' above.)

- Meningiomas are classified according to the World Health Organization (WHO) grading system. WHO grade I lesions are benign and generally have a favorable prognosis, while atypical (grade II) and malignant (grade III) meningiomas are substantially more likely to recur. (See 'WHO classification' above.)

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## GRAPHICS

### Distribution of all primary brain and CNS tumors by site

<table>
<thead>
<tr>
<th>Histology</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumors of neuroepithelial tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>2625</td>
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<tr>
<td>Protoplasmic and fibrillary astrocytoma</td>
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<td>Anaplastic astrocytoma</td>
<td>3385</td>
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<tr>
<td>Unique astrocytoma variants</td>
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<td>17.1</td>
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<td>Oligodendroglioma</td>
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<td>Choroid plexus</td>
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<td>Neuroepithelial</td>
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<td>Embryonal/primitive/medulloblastoma</td>
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<td><strong>Tumors of cranial and spinal nerves</strong></td>
<td>13,735</td>
<td>8.7</td>
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<td>Nerve sheath, non-malignant and malignant</td>
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<td><strong>Tumors of meninges</strong></td>
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<td>Meningioma</td>
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<td><strong>Lymphomas and hematopoietic neoplasms</strong></td>
<td>3855</td>
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<tr>
<td>Lymphoma</td>
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<tr>
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<td>Germ cell tumors, cysts and heterotopias</td>
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<tr>
<td><strong>Tumors of sellar region</strong></td>
<td>21,287</td>
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</tr>
<tr>
<td>Tumor Type</td>
<td>Cases</td>
<td>Percentage</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-------</td>
<td>------------</td>
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<tr>
<td>Pituitary</td>
<td>20,131</td>
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<tr>
<td>Craniopharyngioma</td>
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<td>Chordoma/chondrosarcoma</td>
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<td>Neoplasm, unspecified</td>
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<td>4.7</td>
</tr>
<tr>
<td>All other</td>
<td>76</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>158,088</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Incidence rates of primary brain tumors by major neuroepithelial tissue and meningeal histologic types and age group, CBTRUS, 1992-1997

The category All Brain Tumors includes some specific types not individually shown (tumors of cranial and spinal nerves, hemangioblastomas, primary lymphomas, germ cell tumors, and tumors of the sellar region). The Astrocytoma category includes diffuse astrocytomas, anaplastic astrocytomas, unique astrocytoma variants, and astrocytomas not otherwise specified.

PNET: primitive neuroectodermal tumor.

## Meningioma subtypes

<table>
<thead>
<tr>
<th>Meningiomas with low risk of recurrence or aggressive growth:</th>
<th>WHO grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningothelial</td>
<td>I</td>
</tr>
<tr>
<td>Fibrous (fibroblastic)</td>
<td>I</td>
</tr>
<tr>
<td>Transitional (mixed)</td>
<td>I</td>
</tr>
<tr>
<td>Psammomatous</td>
<td>I</td>
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<tr>
<td>Angiomatous</td>
<td>I</td>
</tr>
<tr>
<td>Microcystic</td>
<td>I</td>
</tr>
<tr>
<td>Secretory</td>
<td>I</td>
</tr>
<tr>
<td>Lymphoplasmacyte-rich</td>
<td>I</td>
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<tr>
<td>Metaplastic</td>
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<table>
<thead>
<tr>
<th>Meningiomas with greater likelihood of recurrence and/or aggressive behavior:</th>
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<tbody>
<tr>
<td>Atypical</td>
<td>II</td>
</tr>
<tr>
<td>Clear cell (intracranial)</td>
<td>II</td>
</tr>
<tr>
<td>Chordoid</td>
<td>II</td>
</tr>
<tr>
<td>Rhabdoid</td>
<td>III</td>
</tr>
<tr>
<td>Papillary</td>
<td>III</td>
</tr>
<tr>
<td>Anaplastic (malignant)</td>
<td>III</td>
</tr>
<tr>
<td>Meningiomas of any subtype or grade with high proliferative index and/or brain invasion</td>
<td></td>
</tr>
</tbody>
</table>

WHO: World Health Organization.
Histologic appearance of meningioma, WHO grades I-III

Left panel: transitional meningioma (grade I) showing characteristic cellular whorls; intranuclear pseudo-inclusions are visible in some cells. Middle panel: Chordoid meningioma (grade II) with cohesive epithelial-like cords of cells; small foci of more typical arachnoidal differentiation are found in most of these tumors. Right panel: anaplastic meningioma (grade III) consisting of pleomorphic arachnoidal cells with a high mitotic rate; foci of necrosis are widely distributed throughout most anaplastic meningiomas.
