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Low-Grade Gliomas

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Continuing Education Activity

Low-grade gliomas are primary brain tumors characterized by slow growth but inevitable progression over time. Median survival ranges from 2 to more than 12 years, influenced by patient age, tumor type, molecular markers, and extent of resection. Prognostic factors, such as younger age, seizure at presentation, 1p/19q-codeletion, and *IDH* mutation, are associated with more favorable outcomes. In contrast, tumor size, midline involvement, *CDKN2A* deletions, and residual disease after surgery predict a poorer prognosis. Management strategies include surgery, radiotherapy, chemotherapy, and emerging targeted therapies such as IDH inhibitors. Surveillance imaging is essential, with frequency tailored to initial treatment and recurrence risk. Despite advances in surgery and radiotherapy, complications such as seizures, cognitive impairment, and treatment-related toxicities remain common, underscoring the need for long-term follow-up and supportive care. Patient education and shared decision-making are integral to optimizing quality of life.

Participants learn to recognize clinical and molecular prognostic factors that guide the management of low-grade gliomas, interpret evolving evidence for systemic and targeted therapies, and apply strategies to mitigate treatment-related complications. Competence improves in tailoring surveillance intervals, counseling patients about long-term outcomes, and integrating novel therapeutic options. Collaboration with an interprofessional team, including neurosurgery, neuro-oncology, radiation oncology, neurology, radiology, pathology, rehabilitation, pharmacy, and supportive care services, enhances coordination, reduces complications, and promotes shared expertise during decision-making. Highlighted is effective interprofessional collaboration, which supports individualized care, enhances patient education, and improves outcomes for individuals with low-grade gliomas, including survival and quality of life.

Objectives:

- Apply prognostic and molecular markers to guide individualized management strategies for patients with low-grade gliomas in collaboration with the interprofessional healthcare team.

- Evaluate the risks, benefits, and sequencing of surgery, radiotherapy, chemotherapy, and targeted therapies to optimize outcomes while communicating treatment plans effectively across neurosurgery, oncology, and other disciplines.
- Differentiate between tumor progression and treatment-related toxicities using advanced imaging modalities.
- Implement evidence-based surveillance protocols and supportive care strategies, improving patient counseling and reinforcing collaboration among neurologists, rehabilitation specialists, pharmacists, and other healthcare professionals.

Introduction

Tumors of the central nervous system (CNS) are classified according to the cell lineage of origin. Gliomas are neuroepithelial tumors that originate from glial cells within the CNS. Glial tumors are further classified based on the cell types involved, such as astrocytomas, ependymomas, and oligodendrogliomas. This review focuses on diffuse gliomas of low-grade pathology, specifically World Health Organization (WHO) grade 2 (diffuse infiltrating) gliomas.

In 2016, the WHO introduced a revised classification of CNS tumors that incorporated molecular profiling in addition to histopathology for the first time. In 2021, the WHO updated its classification of these tumors, some of which were diagnosed solely based on their genetic characteristics. Gliomas are now classified into 3 subtypes: *isocitrate dehydrogenase* (IDH)–mutant astrocytomas, IDH-mutant and 1p/19q-codeleted oligodendrogliomas, and IDH–wildtype glioblastoma. IDH-mutant astrocytomas are assigned WHO grades 2 through 4, with the distinction between WHO grades 2 and 3 based on mitotic activity. IDH-mutant astrocytomas that harbor mutations in *CDKN2A/B* are automatically designated WHO grade 4 astrocytomas. Oligodendrogliomas, IDH-mutant, and 1p/19q-codeleted tumors can be WHO grade 2 or 3.[3]

The histologic grading is based on cytological atypia, mitotic activity, anaplasia, microvascular proliferation, and necrosis. High-grade gliomas demonstrate all these characteristics, whereas low-grade gliomas (LGGs) typically exhibit only cytological atypia or none of the other findings. LGGs generally are slower-growing tumors compared to high-grade gliomas. However, more than 70% transform into a higher grade or become aggressive within a decade. Pretreatment MRI study results have shown that LGGs typically grow at an average rate of 4.1 mm annually. Survival rates are favorable for low-grade gliomas compared to more aggressive grades. Thus, various factors should be considered, including the toxicity of chemotherapy, radiation therapy, and complications of surgical interventions, to manage LGGs and improve outcomes appropriately.

Etiology

LGGs do not have a known, well-established etiology, and the risk factors associated with their development are poorly understood. Therapeutic irradiation is the only major environmental factor that increases the risk of all brain tumors, including LGGs. Factors such as diets

containing N-nitroso compounds, exposure to environmental carcinogens, and occupational hazards have been linked to sporadic mutations, including those affecting the tumor protein p53. However, some hereditary mutations are more frequently identified in gliomas. Conversely, brain tumors are present in various inherited tumor-predisposing syndromes like neurofibromatosis, Li-Fraumeni cancer syndrome, and Lynch syndrome. Notably, these syndromes constitute a small proportion of all glioma cases.

Epidemiology

The precise incidence of low-grade gliomas remains uncertain following the adoption of the 2016 WHO CNS classification because tumor registries are still ongoing. Based on study results conducted using the previous classification, the incidence was 0.25 per 100,000 person-years for grade 2 oligodendrogliomas, 0.51 per 100,000 person-years for astrocytomas, and 0.20 per 100,000 person-years for mixed gliomas in the United States. Low-grade gliomas occur more commonly in individuals between 20 and 40.[9] The peak incidence of oligodendrogliomas is between 40 and 45 years, and 30 to 40 years for astrocytomas. Furthermore, low-grade gliomas are slightly more common in men.

Pathophysiology

Multiple acquired genetic mutations are found in gliomas. Tumor suppressor protein 53 (p53), phosphatase and tensin homolog, and epidermal growth factor receptor (*EGFR*) are involved in the pathogenesis of these tumors. The p53 protein is called the "guardian of the genome" and ensures the DNA is copied correctly, destroying the cell if it is mutated. The gene for p53, *TP53,* usually mutates early in tumorigenesis, allowing other mutations to accumulate. The *EGFR* gene typically stimulates cells to divide, but when amplified, it stimulates cells to divide uncontrollably. Together, these mutations cause increased cell division, a hallmark of cancer.

LGGs grow slowly and may be monitored over several years without treatment unless they become symptomatic. The most common presenting symptom of LGGs is headache. As tumors enlarge, they can cause a mass effect on the adjacent brain structures. The headache is caused by increased pressure in the microvasculature resulting from obstruction, which leads to hydrocephalus. Other symptoms due to obstructive hydrocephalus include changes in vision, nausea, and vomiting. Seizures are another common symptom resulting from cortical hyperexcitability due to the diffuse infiltration of tumor cells.

Histopathology

Cytologic atypia, anaplasia, microscopic proliferation, and necrosis are the histologic features used to differentiate low-grade from high-grade gliomas. Well-differentiated and hypercellular glia with nuclear atypia and rare mitotic activity are the histologic features of LGGs. The tumor type is classified based on the cellular morphology (eg, the "fried-egg" appearance of oligodendrogliomas). Pleomorphic giant cells are present in oligodendrogliomas and astrocytomas, respectively.

History and Physical

The presenting symptoms are determined by the tumor's location in the brain. For example, behavioral changes may occur with frontal lobe tumors, receptive aphasia with temporal lobe tumors, and variable presentations with parietal lobe tumors. However, LGGs are relatively less likely to present with focal neurological deficits such as unilateral weakness or aphasia. These tumors tend to infiltrate rather than destroy or compress the cortex, resulting in a lack of functional deficit. Cognitive dysfunction may develop over time and is primarily related to tumor location and size.

The most common presenting symptoms of low-grade gliomas are headache and seizures. Seizures are more prevalent in oligodendrogliomas because they tend to invade the cortex. Seizures can be either partial/focal or generalized tonic-clonic. Focal seizures may be unrecognized, delaying diagnosis. As the tumor enlarges, there is a rise in intracranial pressure. Headaches manifest due to the increased pressure in the microvasculature and obstruction of the vessels. Other symptoms due to the elevated intracranial pressure are changes in vision, nausea, and vomiting. Patients can also be asymptomatic, especially if obstruction or compression is absent. A comprehensive physical examination can assess for focal neurological deficits and systemic involvement, especially in genetic predisposition syndromes. For example, papilledema may be evident on fundoscopy.

Evaluation

The results of imaging studies vary according to the type and grade of the tumor. After imaging evaluation, surgery is typically indicated for large tumors causing neurologic deficits and to obtain a tissue sample for histopathologic and molecular testing.

Radiologic Evaluation

Computed tomography scan: A CT scan is typically the initial study performed in the acute setting. On CT scans, low-grade tumors usually appear as low-density lesions. Over 95% of these tumors are located in the supratentorial compartment, most often in the frontal or temporal lobes. Calcification occurs in about 20% of these tumors, particularly in oligodendrogliomas. Contrast enhancement is uncommon; when present, it is patchy rather than the typical ring-enhancing appearance seen in high-grade gliomas.

Magnetic resonance imaging: MRI is a more sensitive imaging study than CT for delineating low-grade tumors and soft tissue. Low-grade gliomas appear hypointense on T1 and hyperintense on T2-fluid attenuated inversion recovery (FLAIR) sequences. Calcification is often evident on susceptibility-weighted imaging sequences, especially in oligodendrogliomas. Low-grade tumors typically do not demonstrate enhancement, but may have patchy areas. Because contrast enhancement reflects a breach in the blood-brain barrier, its presence would indicate a more aggressive or higher-grade tumor. First reported in 2017, the T2-FLAIR mismatch sign is a particular biomarker for *IDH*-mutant, 1p/19q non-codeleted tumors. This sign is characterized by a complete hyperintense signal of the tumor on T2-weighted imaging with a relative hypointensity on FLAIR images except for a hyperintense rim

on the periphery. Results from a meta-analysis reported a pooled sensitivity of 40% and a pooled specificity of 100% for these imaging findings. Park et al reported a more comprehensive review of imaging findings in diffuse gliomas.

Advanced imaging techniques , including functional MRI, diffusion MRI, perfusion MRI, MR spectroscopy, and positron emission tomography (PET) scans, provide additional diagnostic information, helping to identify and grade gliomas and monitor disease progression. These tests are not routinely performed but help characterize higher-grade gliomas in cases where conventional MRI is inconclusive. These specialized tests help identify changes in the tumor and its surrounding microenvironment, allowing for the monitoring of treatment response and disease progression. In PET scans, accumulation of fluorodeoxyglucose F18 can help to distinguish low-grade from high-grade gliomas based on the level of uptake. Other radiolabeled amino acids are also used for tumor imaging.

Neuropathologic Diagnosis

Updated guidelines recommend histopathologic examination and testing for specific genetic mutations to ensure an accurate diagnosis.

Histopathology: The main histopathologic features that classify brain tumors include atypia, anaplasia, microvascular proliferation, and necrosis. Low-grade gliomas are well-differentiated and demonstrate hypercellular glial cells, nuclear atypia, and rare mitotic activity. The Ki-67 labeling index, an indicator of mitotic activity, is typically below 10% in low-grade gliomas. Furthermore, the appearance of the cells depends on the type of tumor. Oligodendrogliomas tend to have a classic "fried-egg appearance" with clear, scant cytoplasm, isomorphic round nuclei, and fine, delicate branching vessels, sometimes described as "chicken wire vasculature." Astrocytomas are characterized by pleomorphic giant cells with prominent cytoplasmic processes creating a fibrillary stroma, and stain intensely with vimentin and glial fibrillary acidic protein.

Molecular neuropathology: Major revisions to the WHO classification in 2016 and 2021 have incorporated molecular neuropathology findings into classifying low-grade gliomas. For example, *TP53* mutations are present in most low-grade astrocytomas and are rare in oligodendrogliomas. Most oligodendrogliomas demonstrate a codeletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). These alterations (*TP53* and 1p/19q-codeletion) are mutually exclusive in almost all low-grade gliomas. Mutations in *IDH,* which encodes an enzyme in the Krebs cycle, are present in more than 75% of low-grade gliomas. Most are *IDH1* mutations (*R132H*) with less common *IDH2* mutations. These mutations lead to altered enzyme function, resulting in increased production of the oncometabolite 2-hydroxyglutarate, broadly affecting gene expression. Thus, from a molecular neuropathology perspective, low-grade gliomas may be classified into 3 categories: 1) *IDH* mutations with 1p/19q-codeletion, usually in oligodendrogliomas, 2) *IDH* mutations without 1p/19q-codeletion, usually present in astrocytomas with *TP53* and *ATRX* mutations, and 3) neither *IDH* mutation nor 1p/19q-codeletion.

Thus, when a glioma is suspected based on clinical presentation, imaging, and biopsy results, it is strongly recommended to test for *IDH* mutation and 1p/19q-codeletion for definitive tumor classification. In the 2016 WHO CNS classification, the diagnosis of oligoastrocytoma was strongly discouraged because molecular studies almost always allowed classification of either oligodendroglioma or astrocytoma. Subsequently, in the 2021 WHO CNS update, the diagnosis of oligoastrocyoma was formally removed as a diagnostic category.

Treatment / Management

After presenting with clinical symptoms and imaging findings compatible with a low-grade glioma, the need for surgical resection is the initial consideration. Surgery is indicated in patients with significant mass effect and neurological deficits and is recommended over observation or biopsy to improve overall survival. The major challenge arises when tumors are discovered incidentally, such as in an individual presenting with a seizure or headache. Often, seizures can be medically treated, allowing for careful monitoring before initiating treatment.

Multiple factors must be considered when determining the appropriate management, including the patient's preference and prognostic factors such as age, tumor size, and location. Adjuvant treatment with radiotherapy and chemotherapy may be considered in patients at high risk of recurrence based on age and extent of resection. The recently updated guidelines from the Congress of Neurological Surgeons recommend chemotherapy as a strategy to delay the use of radiation and as an adjunct to radiation in those who cannot undergo gross total resection. If observation is chosen for low-risk cases, serial imaging should be performed as part of a surveillance protocol.

Differential Diagnosis

Because multiple conditions can present similarly to low-grade gliomas, several differential diagnoses must be considered, including:

- Acute disseminated encephalomyelitis
- Brain abscess
- Cavernous malformation
- Cavernous sinus syndrome
- Cerebral metastasis
- Intracranial hemorrhage
- Meningioma
- Primary CNS lymphoma
- Progressive multifocal leukoencephalopathy

- Spinal tuberculosis
- Stroke

Surgical Oncology

Surgical resection in eligible patients is the cornerstone of treatment for low-grade gliomas. Despite lacking level I evidence, resection serves diagnostic and therapeutic purposes, providing sufficient tissue to confirm the diagnosis and facilitate molecular testing. Resection relieves mass effect, hydrocephalus, and edema. The extent of resection (EOR) impacts overall and progression-free survival. For patients with more than 90% EOR, the 5-year overall survival is 97% compared with 76% for those with less than 90% EOR. Most experts favor maximal safe resection over biopsy. More recent study results have shown improved overall survival for patients with an EOR greater than 75% and progression-free survival for patients with an EOR greater than 80%. Moreover, diagnostic accuracy is greater with resection than with needle biopsies. Needle biopsies with observation have been associated with decreased overall survival compared with early resection.

Supramaximal resection is controversial in the literature and involves surgical resection of the tissue beyond the FLAIR signal abnormalities. Proponents of supramaximal resections argue that tumor cells can infiltrate the brain parenchyma beyond the FLAIR signal abnormality. In contrast, other experts are concerned about iatrogenic injury to the surrounding brain. The Congress of Neurological Surgeons' guidelines recommend maximal safe resection to improve progression-free and overall survival in patients with *IDH*-mutant WHO grade 2 diffuse gliomas. However, there is insufficient evidence that maximal resection improves overall survival in patients with 1p/19q-codeleted oligodendrogliomas. The Response Assessment in Neuro-Oncology group has proposed an algorithm to estimate patient outcomes with newly diagnosed gliomas.

There are multiple techniques to prevent neurological deficits during gross total resection of the tumors for extended surgery or when tumors are not well-demarcated. These techniques include stereotactic neuronavigation, intraoperative MRI, fluorescence-guided glioma surgery, and intraoperative functional mapping. Intraoperative MRI (iMRI), developed in the 1990s, is one of the more established techniques for tumor identification, maximizing tumor resection through real-time imaging. The technique provides real-time accuracy, considering brain shifts from edema, loss of cerebrospinal fluid, and tumor removal. Randomized trials comparing iMRI with more conventional microsurgery with neuronavigation demonstrated 96% complete tumor resection using iMRI compared to 68% with conventional techniques, although no difference in progression-free survival was observed. Furthermore, no additional surgical morbidity was demonstrated with iMRI. The updated guidelines from the Congress of Neurological Surgeons suggest that iMRI or intraoperative ultrasound can be used to increase tumor resection compared to conventional techniques such as intraoperative navigation.

Other methods to maximize resection include heme precursor 5-aminolevulinic acid (5-ALA), which is transformed into protoporphyrin IX, a compound that fluoresces red under blue light. This technique leverages the difference in blood-brain barrier integrity between infiltrating

tumors and healthy brain tissue and differential heme biosynthesis. Patients are given 5-ALA orally or intravenously and, after several hours, accumulate protoporphyrin IX, which can be detected during surgery in areas of residual tumor. Most prospective data for this technique pertain to high-grade gliomas, demonstrating improvement in progression-free survival and higher tumor resection rates. However, this technique has low detection rates in low-grade gliomas, ranging from 0% to 35%. Currently, this technique is not approved for LGGs and does not improve the extent of resection in grade 2 gliomas.

Intraoperative functional mapping includes several techniques with the common goal of minimizing postoperative morbidity. The awake craniotomy for functional mapping is a technique with level 3 evidence that can increase the extent of resection. Once the skin incision and craniotomy are completed, sedation is discontinued, and direct cortical or subcortical stimulation is performed. Direct stimulation of neurons is performed using a bipolar stimulation device. Language testing is then performed, and patients are evaluated for speech arrest, anomia, alexia, and dysarthria, which are then mapped intraoperatively. “Negative” functional mapping is the more common technique. A functional map is generated based on cortical stimulation that fails to produce a neurologic deficit. This technique enables smaller craniotomies, shorter operative times, and fewer postoperative neurological deficits than traditional “positive” mapping.

Stereotactic neuronavigation is commonly used in cranial surgery and allows for a 3-dimensional anatomic reconstruction using cross-sectional imaging such as CT or MRI. This modality is beneficial in preoperative planning, as it tailors craniotomies and surgical approaches to individual needs. However, the lack of real-time adjustments due to edema and changes in cerebrospinal fluid limits its usefulness and typically requires additional functional imaging. MRI diffusion tensor imaging or magnetoencephalography are noninvasive functional mapping tools that can be used with traditional neuronavigation. Randomized trial results with standard neuronavigation with or without MRI diffusion tensor imaging demonstrated approximately 50% reduction in postoperative neurologic deficits (9.8% vs 18.6%) using noninvasive functional imaging.

LGGs can recur years to decades after initial definitive treatment. These patients may present with seizures, new neurologic deficits, or progression on imaging studies. Treatment is controversial, and the data are retrospective. Repeat surgery can be considered when complete resection of the tumor is possible. The extent of resection during the primary and repeat surgery may impact overall survival ; however, the updated guidelines report insufficient evidence regarding the value of the extent of resection in relation to overall survival in this patient population.

In patients with recurrent tumors, temozolomide and the combination of procarbazine, lomustine, and vincristine are recommended, with temozolomide being the initial choice. Furthermore, radiation is suggested in patients who have not had previous radiation and should be strongly considered in those who have undergone prior radiation therapy. Patients with recurrence do not have a decrease in overall survival after multiple

resections. However, diligent preoperative evaluation with adequate imaging determines the probability of a gross total resection while minimizing the postoperative morbidity. Functional mapping or intraoperative molecular imaging is also helpful.

Complications of surgical resection include seizures, epidural hematoma, cerebral abscess, infection, stroke, motor deficits, sensory deficits, speech deficits, partial blindness, and behavioral changes. An MRI is performed in the first 24 to 72 hours postoperatively to plan subsequent therapy. Postoperative monitoring can detect any neurological deficits that may occur after the procedure.

Radiation Oncology

The use in low-grade gliomas was evaluated in the 1980s in the European Organisation for Research and Treatment of Cancer study 22845, which compared immediate radiotherapy after resection with salvage. Five-year progression-free survival was 55% in the radiotherapy group versus 35% in the control group, but no survival benefit was observed. In addition, a reduction in seizure activity (25% vs 41%) was also noted, with no significant difference in malignant transformation. However, dose escalation trial results have not shown progression-free or overall survival benefits.

The role of radiotherapy in the setting of low-grade glioma is restricted to patients at high risk of progression despite surgery. The National Comprehensive Cancer Network guidelines recommend radiotherapy for patients older than 40 or those undergoing subtotal resection. Prognostic factors were gleaned from the European Organisation for Research and Treatment of Cancer study 22845 that aid in the decision to offer adjuvant radiotherapy. These factors include tumor size larger than 6 cm, age older than 40 years, a tumor crossing the midline, astrocytoma histology, and neurologic deficits. Patients with 3 or more risk factors are considered high-risk and may benefit from adjuvant radiotherapy.

For high-risk tumors, radiotherapy is typically combined with chemotherapy. Radiation Therapy Oncology Group study 9802 examined 6 cycles of procarbazine, lomustine, and vincristine (PCV) in high-risk WHO grade 2 gliomas. Results demonstrated a significant improvement in median survival (13.3 vs 7.8 years) and 10-year progression-free survival (51% vs 21%). Subgroup analysis revealed that chemotherapy's benefits were confined to *IDH*-mutated gliomas. Other agents, such as temozolomide (TMZ), have also been investigated. Results from a phase 2 trial using concurrent and adjuvant TMZ demonstrated a 5-year overall survival of 61%, with 54% of patients experiencing a grade 3 to 4 toxicity.

The ongoing CODEL trial, which includes high-risk WHO grade 2 gliomas and grade 3 gliomas with 1p/19q-codeletion, is a randomized prospective trial comparing PCV to TMZ with the use of radiotherapy in both arms (NCT00887146). A third TMZ arm was terminated prematurely due to the extremely high rates of progression. Furthermore, the updated guidelines from the American Society of Clinical Oncology and the Society for Neuro-Oncology recommend that patients with oligodendrogliomas, *IDH*-mutated, 1p/19q-codeleted, CNS WHO grade 2 tumors

should be offered radiation therapy in addition to PCV. Similarly, patients with astrocytoma, *IDH*-mutant, 1p/19q non-codeleted, CNS WHO grade 2 tumors should receive radiation in addition to chemotherapy.

The timing and sequencing may vary depending on the systemic agent. If PCV is planned, radiotherapy is typically administered before chemotherapy. If TMZ is used, radiotherapy is delivered concurrently. Results from a Cochrane review reported equivocal findings in overall survival for patients receiving early versus delayed radiotherapy. However, patients undergoing early radiation therapy demonstrated more extended remission than those receiving delayed radiation.

Simulation Setup

Before CT simulation, the patient is typically placed in the supine position with head immobilization and a thermoplastic head mask. Preoperative and postoperative MRI of the brain with and without contrast should be fused with the CT images to improve target delineation, including the tumor bed, gross residual disease, and residual edema.

Delivery

The 2 most common modalities are intensity-modulated radiation therapy and proton therapy. Intensity-modulated radiation therapy is beneficial due to the low radiation dose and the sparing of critical structures, reducing the risk of long-term adverse effects. Proton therapy can be used in certain circumstances, especially in children, to reduce the radiation dose to critical structures and potentially reduce long-term toxicity. Results from a meta-analysis showed comparable survival outcomes with proton therapy versus conventional radiotherapy.

Dose and Dose Constraints

Doses typically range from 45 to 54 Gy in 1.8 to 2.0 Gy per fraction. Doses above 45 Gy have not demonstrated a progression-free or overall survival benefit. Organs at risk include the lens, lacrimal gland, retina, optic nerve, optic chiasm, brain stem, spinal cord, pituitary gland, cochlea, and uninvolved brain tissue. Minimizing radiation to these structures, especially the CNS organs, is critical to reducing the risk of neurocognitive decline and radionecrosis. While specific protocols may vary in dose recommendations, the Quantitative Analysis of Tissue Effects in the Clinic guidelines are acceptable. The brainstem dose goal should be below 54 Gy, keeping the necrosis rate below 5%.

The optic nerve/chiasm radiation dose should be less than 55 Gy, which has less than 3% risk of neuropathy. Spinal cord radiation doses of 50 Gy or less carry a less than 1% risk of myelopathy. Cochlear mean radiation doses of less than 45 Gy generally have less than a 30% risk of hearing loss. Radiation doses to the uninvolved brain areas should be less than 60 Gy to reduce the risk of symptomatic necrosis to less than 3%. Radiation doses to the lens should be less than 5 to 7 Gy. The dose to the retina should be less than 45 to 50 Gy. The pituitary radiation dose should be less than 45 Gy, but in younger patients, the dose should be less than 30 Gy.

Target Delineation

MRI imaging is critical for target delineation. The preoperative and postoperative MRI scans should be fused with the planning CT. Preoperative imaging can help define the tumor bed, while postoperative imaging detects any residual disease and edema. The gross target volume is any residual disease based on the operative report or imaging. The clinical target volume includes the gross target volume, the tumor bed, and any postoperative edema on the T2/FLAIR MRI sequence. A 1 to 1.5cm margin is typically added to make the gross target volume, with an additional 0.5 to 0.7 cm margin.

Re-irradiation

One prospective study evaluated patients younger than 40 who had undergone a gross total resection of a low-grade glioma. The results found that approximately 50% had a recurrence within 5 years after surgery. Radiotherapy can be used in recurrent LGGs when a gross total resection is not feasible or as adjuvant therapy after a high-risk resection. Previous radiotherapy fields dictate dosing, fractionation, and the volume receiving the additional dose. Stereotactic radiosurgery, body radiation therapy, and more fractionated approaches can also be considered.

Medical Oncology

The number of systemic agents available in low-grade gliomas is limited because the blood-brain barrier prevents higher concentrations of these agents from entering the CNS. Targeted therapies also have a role in treating some of these malignancies. Procarbazine, lomustine, and vincristine (PCV), typically administered as adjuvant therapy after radiotherapy or surgery, is one of the original treatment regimens investigated. Radiation Therapy Oncology Group study 9802 examined adjuvant PCV after radiotherapy in high-risk low-grade gliomas. While the initial results did not show a survival benefit, the long-term results demonstrated a significant increase in 10-year progression-free survival (21% vs 51%) and overall survival (60% vs 40%).

On subanalysis, the benefit appeared to be confined to *IDH*-mutated gliomas. The PCV regimen is being evaluated in prospective trials in more aggressive tumor types, such as in the CODEL trial (NCT00887146). The treatment is typically delivered over 6sixcycles: procarbazine at a dose of 60 mg/m^2/day orally on days 8 to 21 of each cycle, lomustine at a dose of 110 mg/m^2/day orally on day 1 of each cycle, and vincristine at 1.4 mg/m^2 (maximum dose of 2 mg) administered intravenously on days 8 and 29 of each cycle. Toxicities include bone marrow suppression resulting in thrombocytopenia, neutropenia, and anemia, with 45% experiencing severe suppression. Hepatotoxicity, neurotoxicity, allergic drug reactions, nausea, and vomiting have also been documented. The updated recommendations support deferring treatment with PCV in patients with oligodendrogliomas or astrocytomas until there is radiographic or symptomatic progression, especially those with favorable prognostic factors (gross total resection, younger age).

TMZ is an oral alkylating agent that treats low- and high-grade gliomas. TMZ typically alkylates guanine residues at the N-7 or O-6 positions, and can be used alone, in combination with radiotherapy, or as adjuvant treatment after radiotherapy. TMZ is an alternative to PCV if there is a strong concern for toxicity. The efficacy of this medication is impacted by the expression or silencing of the O-6-methylguanine-DNA methyltransferase (*MGMT*) gene. When the gene is expressed in tumor cells, it removes methyl groups from the O-6 position, reversing the drug's effect.

Regardless, National Cancer Comprehensive Network guidelines recommend its use irrespective of *MGMT* methylation status. Radiation Therapy Oncology Group study 0424, a phase 2 trial, evaluated TMZ concurrently and adjuvantly with radiotherapy, which improved the 3-year overall survival rate to 74% compared to 54% in controls. Upon long-term evaluation, the 5- and 10-year overall survival rates were 60.9% and 34.6%, respectively. The drug is delivered at 75 mg/m^2/day concurrently with radiotherapy and 150 mg/m^2 postradiotherapy. The most common toxicities are myelosuppression, nausea, and vomiting. Further, vorasidenib is a dual inhibitor of the *IDH1* and *IDH2* mutated enzymes, significantly improved progression-free survival, and delayed time for subsequent intervention in a double-blinded, phase 3 trial. These results have led to the recommendation for vorasidenib in patients with astrocytomas or oligodendrogliomas after surgical intervention, when further treatment with radiation and chemotherapy can be deferred.

Other targeted therapies, such as *BRAF/MEK* inhibitors, may be suitable for certain gliomas, including pilocytic astrocytomas, pleomorphic xanthoastrocytoma, and ganglioneuromas. Patients undergoing subtotal resection or progressing with *BRAF* V600E activating mutations may be eligible for dabrafenib/trametinib or vemurafenib/cobimetinib. These drugs arrest cell growth by inhibiting *B-Raf* (dabrafenib and vemurafenib) and *MEK* (trametinib and cobimetinib), which are part of the *Ras-Raf-MEK-ERK* pathway that stimulates cell proliferation. A mechanistic target of rapamycin inhibitor such as everolimus may be considered for subependymal giant cell astrocytomas.

In the recurrent disease setting, systemic treatments for recurrent LGG can be considered alone, combined with radiotherapy, or as adjuvant therapy. PCV, TMZ, or lomustine alone can be considered. PCV or TMZ can also be considered after radiotherapy. Platinum-based therapies may also be used in cases of progression after first-line treatments. The TAVAVEC trial is investigating the combination of bevacizumab with TMZ in recurrent WHO grade 2 and 3 gliomas that do not demonstrate any improvement in overall or progression-free survival. Another phase 3 trial compares radiotherapy with adjuvant temozolomide versus radiotherapy with adjuvant PCV in anaplastic or low-grade codeleted gliomas(NCT00887146). Clinical trials evaluating treatments targeting the mutant IDH protein are also underway.

Regardless of the initial management, low-grade gliomas ultimately recur. Increased enhancement might develop on serial images, indicating that the tumor has undergone malignant transformation into a high-grade glioma. The updated Response Assessment in Neuro-Oncology guidelines recommend that the postradiation MRI be used as a baseline, rather than the postsurgical MRI, as pseudoprogression is highest 12 weeks after radiation.

Prognosis

Patients with low-grade gliomas experience a spectrum of outcomes. The median survival ranges from 2 to more than 12 years, depending on the tumor grade. Understanding the prognostic factors is crucial for making informed treatment decisions and patient counseling. The clinical prognostic factors include:

- **Age:** Younger patients have better outcomes than older patients, with some studies classifying the age younger than 40 as low risk and older than 40 as high risk.
- **Symptoms:** Presenting seizures are associated with a favorable prognosis, likely due to earlier diagnosis and closer monitoring. However, these findings could be due to lead-time bias, while fixed neurological deficits are associated with a poor prognosis.
- **Tumor size and location**: Larger tumors or involvement of the corpus callosum are associated with a poor prognosis. Subtotal resection and residual tumor are associated with increased mortality.

Molecular tests allow for a more accurate prognosis. For example, 1p/19q-codeletion is associated with a favorable prognosis. One study's results showed that the median survival of patients with 1p/19q codeleted tumors (oligodendrogliomas) was 12 years, compared to 8 years in noncodeleted gliomas. *IDH* mutation is also associated with a favorable prognosis in most low-grade gliomas. Results from a French study showed an overall survival of 11 years versus 7 years in gliomas with and without *IDH* mutation in low-grade gliomas treated with temozolomide, indicating a favorable prognosis with chemosensitivity. The presence of *CDKN2A* gene deletions is an independent predictor of mortality.

The long-term outcomes depend on the tumor's type, grade, molecular characteristics, the patient's preoperative Karnofsky performance score, and age. Moreover, cancer affects the quality of life by disrupting physical, social, and mental aspects. Results from a systematic review reported higher proportions of patients returning to work after undergoing gross total resections than those undergoing subtotal resections. Results from another study reported a high rate of patients returning to work within 1 year after resection. Finally, cognitive impairment can present in varying degrees and has been reported in nearly 70% of patients.

Complications

Early postoperative seizures are encountered in approximately 20% of patients and are more common with a limited resection. Gliomas tend to progress over time, necessitating regular surveillance. Depending on the treatment, different surveillance strategies have been recommended. For patients who undergo surgery and initial chemoradiation, MRI surveillance every 6 months for those with astrocytomas and every 6 to 9 months for those with oligodendrogliomas is reasonable. For patients who undergo either radiation or chemotherapy alone postresection, surveillance every 3 to 4 months for the first 5 years is recommended. Surveillance imaging should be as frequent as every 2 to 3 months for tumor recurrence. Several complications are associated with radiotherapy, and the severity depends on the duration of the treatment.

Radiation-Induced Effects

Despite advances in cranial radiotherapy delivery, the risk of acute and delayed adverse effects remains. The acute adverse effects include fatigue, headache, nausea, vomiting, dermatitis of the scalp, and alopecia. These symptoms can begin within the first few days of treatment; however, they are rarely severe enough to warrant a treatment break. Typically, these symptoms resolve in the weeks following treatment. The late toxicities are of greater concern, especially in younger patients. These late toxicities can appear anywhere from 3 months to several years after treatment. Potential late toxicities include cognitive decline, radiation necrosis, optic neuropathy, spinal cord myelopathy, hearing loss, cataracts, pituitary insufficiency, and radiation-induced secondary tumors.

Radiation necrosis (RN) is one of the more feared complications of radiation treatment. While this condition can occur as soon as 3 months after radiation treatment, it most commonly occurs 1 to 2 years posttreatment. Common symptoms of RN include cognitive decline, focal neurologic deficits, and seizures. Patients may not exhibit symptoms but may have radiographic changes. The risk of RN depends on the dose, fraction size, and volume irradiated. While the risk of RN appears to be independent of location, it seems certain areas are more susceptible to symptomatic RN than others. Partial brain doses of 60 to 72 Gy delivered in 2 Gy per fraction result in a 1% to 5% risk of symptomatic necrosis. Doses exceeding 60 Gy in low-grade glioma are not beneficial; thus, the risk is still relatively small. Twice daily radiotherapy or fraction sizes greater than 2 Gy per fraction can increase this risk.

Distinguishing RN from tumor progression or pseudoprogression can be difficult. MRI of the brain with contrast is the preferred initial imaging modality. Imaging findings such as rim enhancement, soap-bubble appearance on T1-weighted postcontrast imaging, and high signal on T2-weighted imaging have only a 25% positive predictive value. MR spectroscopy of brain metabolites has been used to measure the choline-creatinine, or choline-n-acetyl aspartate, ratios and has a sensitivity and specificity of 94.1% and 100%, respectively, when the ratio is greater than 1.71.[87] MR perfusion is another method that examines relative cerebral blood flow based on dynamic susceptibility-weighted MRI; however, published data are inconsistent, and the values used vary by acquisition method. PET/CT has also been suggested as a potential imaging modality because necrosis would be hypometabolic compared to surrounding brain tissue. Still, it has not been established as a reliable technique.

The first-line treatment for symptomatic RN is corticosteroids with a gradual taper, substantially reducing inflammation but having significant adverse effects. In treatment-refractory cases, the vascular endothelial growth factor inhibitor bevacizumab may be used, and small study results have shown a 97% radiographic response to treatment with a 79% reduction in symptoms. However, there is a risk of thrombosis and hemorrhage with bevacizumab. Surgical resection reduces mass effect and symptoms in patients with extensive necrosis. Hyperbaric oxygen may be another treatment option, but the efficacy of this treatment is not well established.

Other Radiation Toxicities:

- **Spinal cord myelopathy:** Symptoms range from pain, paresthesia, and decreased motor function to paralysis. The risk is 1% to 10% with doses of conventionally fractionated radiotherapy ranging from 54 to 60 Gy.
- **Brainstem necrosis:** Occurs in less than 5% of patients at doses of 54 Gy in 2Gy per fraction; the risk can increase significantly with doses exceeding 64 Gy.
- **Hearing loss:** Can occur if a temporal lobe tumor is near the cochlea. Mean cochlear radiation doses of less than 45 Gy have a 30% or lower risk of sensorineural hearing loss. Patient factors, such as age, postradiation therapy otitis media, and cerebrospinal fluid shunts, may increase risk.
- **Optic neuropathy:** Characterized by acute monocular vision loss occurring 3 months to 8 years posttreatment. Up to 85% of patients have visual acuity of 20/200 or lower. The risk is less than 3% with doses used for low-grade glioma. Hyperfractionation may help to increase the tolerance of the optic nerve/chiasm. Corticosteroids or hyperbaric oxygen have been used for treatment, but with limited efficacy.
- **Hypopituitarism:** A common long-term complication of head and neck radiotherapy. Symptoms vary based on the hormone deficiency that is produced. Commonly, pituitary insufficiency follows a specific temporal pattern with growth hormone and gonadotropin-releasing hormone deficiencies appearing first, followed by adrenocorticotropic hormone and thyroid-releasing hormone deficiency. Hyperprolactinemia may also develop due to the loss of inhibitory control from the anterior pituitary hormones. Interestingly, central diabetes insipidus is relatively rare. Hypopituitarism usually presents in the first 5 years after treatment, but new deficiencies can appear over the patient’s lifetime. The risk of hypopituitarism becomes appreciable when doses exceed 45 Gy and is very high with doses exceeding 60 Gy. Long-term monitoring of hormone levels is appropriate in these patients. Treatment is typically hormone replacement or exogenous stimulation.
- **Cataracts:** The eye's lens is relatively radiosensitive with a conventionally established threshold dose of 2 Gy in a single fraction and 5 to 7 Gy in a fractionated course. The latency period is inversely proportional to the dose, with an average of 2 to 3 years. The only definitive treatment is surgical correction.
- **Radiation-induced tumors:** While mainly a concern in the pediatric population, as cancer therapies improve, a growing cohort of patients may experience radiation-induced tumors. A recent large-scale retrospective cohort study of patients who received cranial radiotherapy for pituitary or craniopharyngiomas evaluated the effects of a median dose of 45 to 50.4 Gy, similar to the dose for low-grade gliomas. The 20-year cumulative risk was 4% in the radiated group, compared with 2.1% in the nonradiated controls. Most secondary tumors were benign (88%), with meningioma being the most common.

Chemotherapy-Induced Effects

Chemotherapy treatment is associated with alopecia, constipation, flu-like symptoms, and central nervous system toxicity, such as weakness, loss of balance, headache, unsteadiness, drowsiness, or dizziness. Vincristine is associated with neuropathy, while bone marrow suppression is seen with lomustine. Medications used for managing seizures and vasogenic edema are also associated with adverse effects that can impair the quality of life in these patients. In addition, anticonvulsant and radiation treatments can cause cognitive changes that can be difficult to distinguish from those secondary to tumor growth. Long-term corticosteroid use, typically required for managing vasogenic edema, also carries a significant risk.

Postoperative and Rehabilitation Care

Postoperatively, routine monitoring is required to address complications such as wound infection and other surgical complications. Rehabilitative care is needed if neurological deficits occur after extensive resection. Rehabilitation aims to strengthen individuals physically, mentally, and socially by providing support and targeted interventions, enhancing their overall quality of life.

Consultations

Several members of the interdisciplinary team can provide further care, including:

- Medical oncology
- Neurology
- Neuropathology
- Neuroradiology
- Neurosurgery
- Radiation oncology
- Physical, occupational, and speech therapy
- Physical medicine and rehabilitation
- Radiation oncology

Deterrence and Patient Education

Educating patients about the tumor, its grade, potential complications, and available treatments is essential to care. Ongoing follow-up and long-term surveillance are necessary for patients with low-grade gliomas. An interdisciplinary approach to patient care is crucial, and any adverse events during treatment should be promptly managed. Referral to a higher-level treatment center should be pursued if adequate care is unavailable locally. Because the patient

plays a key role in managing low-grade glioma, patient education on the condition and the available treatment options enables them to make informed decisions that improve the overall outcome and quality of life.

Enhancing Healthcare Team Outcomes

Brain tumors are serious conditions that require immediate attention and appropriate treatment. An interprofessional healthcare team is needed to manage these conditions. A collaborative effort among neurosurgeons, neuro-oncologists, radiation oncologists, neuroradiologists, pharmacists, clinicians, and other medical support staff is essential to enhance patient care and achieve a favorable outcome. Important treatment decisions are made through interdisciplinary tumor board conferences, which guide management. Thus, improved team performance and patient education are crucial to managing low-grade gliomas.

Review Questions

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