Brain Tumors: Epidemiology and Current Trends in Treatment

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Rec. Date: Sep 20, 2015; Acc. Date: Sep 26, 2015; Pub. Date: Sep 30, 2015

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Abstract

Background: Brain tumors represent a group of neoplasms arising from brain tissue, each with their own unique biology, prognosis, and treatment. Included in this group are neoplasms not arising from brain parenchyma, which encompass meningiomas, lymphomas, and metastatic disease from other primary sources (often referred to as secondary brain tumors). Despite the diverse group of neoplasms represented, most intracranial tumors follow similar clinical presentations and diagnostic workups.

Methods: This review focuses on primary and secondary brain tumor epidemiology, imaging, and treatment modalities. In addition, we will highlight molecular genetic advances in the field that will help shape future treatment approaches.

Results: Although tumors affecting the Central Nervous System (CNS) are relatively uncommon, they are often very difficult to treat and cause disproportionate morbidity and mortality. Many of these neoplasms are universally fatal and our ability to treat both benign and malignant tumors is still in its infancy. Our lack of effective treatment leaves many of our patients with few options.

Conclusions: The combination of poor prognosis and lack of therapeutic options make further innovation and investigation a priority to improve clinical outcomes for patients suffering from CNS malignancies.

Keywords: Brain tumors; Epidemiology; Treatment; Imaging; Neoplasm metastasis; Radiosurgery; Chemotherapy

Primary Brain Tumors

Classification

The World Health Organization (WHO) classifies brain tumors based on histologic features and presumed cellular origin. In 2007, the WHO updated its Central Nervous System (CNS) classification system to reflect a grading scheme in which the histologic diagnosis directly correlates with the histologic grade of the tumor [1]. Seven major categories of tumors in the CNS have been identified by the WHO classification system (Table 1) and include tumors of neuroepithelial tissue, tumors of cranial and paraspinal nerves, tumors of the meninges, lymphomas and hematopoietic neoplasms, germ cell tumors, tumors of the sellar region, and metastatic tumors.

Epidemiology

Approximately 69,720 new cases of primary CNS tumors are expected to be diagnosed in the United States this year [1]. Of these lesions, roughly 24,620 will be malignant [1]. Although the incidence of primary brain tumors is relatively low compared to other cancer types, primary brain tumors give rise to a disproportionate amount of morbidity and mortality, often causing debilitating impairment to patients’ movement and speech [2,3]. Although primary CNS tumors comprise only 1.4% of all cancers, they are among the most aggressive tumors and result in a combined mortality rate of about 60% [2]. In fact, the five-year survival rate for primary malignant brain and central nervous system tumors is the sixth lowest among all types of cancers after pancreatic, liver & intrahepatic bile duct, lung, stomach, and esophageal [2].

The majority of primary brain tumors fall under the WHO classification scheme of tumors of neuroepithelial tissue. Malignant gliomas are the most common primary brain tumor, comprising more than 80 percent of all primary brain neoplasms [4]. Gliomas can be divided into astrocytomas, oligodendrogliomas, ependymomas, and oligo-astrocytomas (mixed gliomas). These neoglial tumors can be further divided based on grade. Astrocytomas are subdivided into grades I-IV as follows: pilocytic, grade I; diffuse, grade II; anaplastic, grade III; and Glioblastoma Multiforme (GBM), grade IV. Ependymomas are subdivided into grades I-III. Oligodendrogliomas are typically grade II and oligoastrocytomas are usually grade III.

Tumors of Neuroepithelial Tissue | Microcystic (WHO grade I)
Table 1: Classification of brain tumors.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Astrocytic tumors</td>
<td>Secretory (I)</td>
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<tr>
<td>Pilocytic astrocytoma (WHO grade I)</td>
<td>Lymphoplasmacyte-rich (I)</td>
</tr>
<tr>
<td>Diffuse astrocytoma (WHO grade II)</td>
<td>Metaplastic (I)</td>
</tr>
<tr>
<td>Anaplastic astrocytoma (WHO grade III)</td>
<td>Chordoid (II)</td>
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<tr>
<td>Glioblastoma (WHO grade IV)</td>
<td>Clear cell (II)</td>
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<tr>
<td>Oligodendrogial tumors</td>
<td>Atypical (II)</td>
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<tr>
<td>Oligodendroglioma (WHO grade II)</td>
<td>Papillary (III)</td>
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<tr>
<td>Anaplastic oligodendroglioma (WHO grade III)</td>
<td>Rhabdoid (III)</td>
</tr>
<tr>
<td>Ependymomas</td>
<td>Anaplastic meningioma (III)</td>
</tr>
<tr>
<td>Myxopapillary (WHO grade I)</td>
<td>Tumors of the Sellar Region</td>
</tr>
<tr>
<td>Subependymoma (WHO grade I)</td>
<td>Pituicytoma (posterior pituitary tumor) (WHO grade I)</td>
</tr>
<tr>
<td>Classic ependymoma (WHO grade II)</td>
<td>Pituicytoma (anterior pituitary tumor) (WHO grade I)</td>
</tr>
<tr>
<td>Cellular</td>
<td>Spindle cell oncocytoma of the adenohypophysis (WHO grade II)</td>
</tr>
<tr>
<td>Papillary</td>
<td>Lymphomas and Haematopoietic Neoplasms</td>
</tr>
<tr>
<td>Clear</td>
<td>Malignant lymphomas</td>
</tr>
<tr>
<td>Mixed Gliomas</td>
<td>Tumors of Cranial and Paraspinal Nerves</td>
</tr>
<tr>
<td>Oligoastrocytomas (WHO grade II)</td>
<td>Schwannoma</td>
</tr>
<tr>
<td>Anaplastic oligoastrocytoma (WHO grade III)</td>
<td>Neurofibroma</td>
</tr>
<tr>
<td>Medulloblastoma (WHO grade IV)</td>
<td>Dermal (WHO grade I)</td>
</tr>
<tr>
<td>Tumors of the Meninges</td>
<td>Plexiform (WHO grade I)</td>
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<tr>
<td>Meningioma</td>
<td>Germ Cell Tumors</td>
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<td>Meningothelial (WHO grade I)</td>
<td>Metastatic Tumors</td>
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<tr>
<td>Fibrous (WHO grade I)</td>
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<tr>
<td>Transitional (WHO grade I)</td>
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<td>Psammomatous (WHO grade I)</td>
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<tr>
<td>Angiomatous (WHO grade I)</td>
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Table 2: Risk factors associated with brain tumors

- Ionizing radiation
- Electromagnetic radiation
- Cell phones and radiofrequency radiation
- Head trauma
- Allergies
- Diet and vitamins
- N-nitroso compounds
- Fat intake
- Aspartame ingestion
- Tobacco
- Alcohol
- Chemicals
- Hair dyes and sprays
- Traffic-related air pollution
- Infection
- Simian Virus 40
- Human Cytomegalovirus
- Polyomaviruses (e.g. JC and BK)
- Toxoplasma infection
- Varicella zoster – protective role
- Genetics
- Neurofibromatosis type 1
- Neurofibromatosis type 2
- Von Hippel-Lindau syndrome
- Li-Fraumeni syndrome
- Turcot syndrome
- Basal cell nevus syndrome
- Adenomatous polyposis syndrome
- Occupational Exposure
- Electrical workers and electromagnetic fields
- Agriculture workers exposed to pesticides, herbicides and fungicides
- Other industries (vinyl chloride, petrochemical, and rubber industries
- Only proven risk factors

Of the gliomas, GBMs (WHO-grade IV) account for 60-70%, anaplastic astrocytomas (WHO-grade III) account for 10-15%, anaplastic oligodendrogliomas (WHO-grade II) and anaplastic...
oligodendrocytomas (WHO-grade III) together comprise 10%. The last 5-20% represent tumor types that are less common including anaplastic ependymomas and anaplastic gangliogliomas [5].

Risk Factors

Several studies have investigated risk factors for brain tumors, but our knowledge of their etiology remains limited. While the only clear risk factor that has been identified for glial and meningeal neoplasms is ionizing radiation [6], some investigators have observed associations to support potential risk factors for primary brain tumors (Table 2). Many occupational studies have been conducted to determine the relative risk of brain tumors with no definitive association to specific chemicals or exposures [7,8]. Evidence of radiation exposure (e.g., electromagnetic radiation and cellular telephones and radiofrequency radiation), other than ionizing, increasing the risk for developing a primary brain tumor is inconclusive [7]. Assessment of additional risk factors including head trauma, allergies, diet, tobacco, and alcohol have also yielded conflicting results with increased risk for developing primary brain tumors [7]. In parallel with these studies, exploration of viral and genetic causes is burgeoning.

Viruses

The relationship between viruses and the development of primary brain tumors is complex and unclear. Several viral families, including Polyomaviruses and Herpesviruses have been associated with brain tumor development. An incident with SV40 contamination in polio vaccines between 1955 and 1963 spurred investigations into SV40 and cancer risk [9]. Interest in SV40 and brain tumor development was motivated by both animal experiments demonstrating brain tumor formation after inoculation with SV40 and the observation of SV40 isolated from human brain tumor tissue [10]. However, a study conducted by Strickler and colleagues showed no difference in the risk of brain tumors between people who received vaccines contaminated with SV40 and those who did not receive the vaccinations [11]. Other polyomaviruses studied in brain tumors include JC and BK viruses [7].

In recent years, an association of Human Cytomegalovirus (HCMV) and GBMs has been investigated with mixed results [12-17]. Due to the high degree of discordance in the literature, the role of HCMV and GBMs is still unclear.

Genetics

Several inherited genetic syndromes have been associated with primary brain tumor development. According to a review conducted by Bondy and colleagues several hereditary syndromes including neurofibromatosis types 1 and 2 (NF1 and NF2), tuberous sclerosis, nevoid basal cell carcinoma syndrome, Turcot syndrome, Li-Fraumeni syndrome and von-Hippel-Lindau (VHL) syndrome all pose a genetic predisposition to brain tumor development [18]. Both NF1 and NF2 will be discussed in more detail in the vestibular schwannoma section. Tuberous sclerosis is a genetic disease affecting multiple systems and is associated with benign tumors of the brain and other vital organs [19].

Nevoid basal cell carcinoma syndrome also affects multiple systems in the human body and is associated with increased risk of medulloblastoma [20]. Turcot syndrome, also known as mismatch repair cancer syndrome due to the association of biallelic DNA mismatch repair mutations, is associated with several symptoms including brain tumors (medulloblastomas and gliomas) and colonic polyposis [21]. Li-Fraumeni syndrome is an autosomal dominant trait that is usually associated with an inherited mutation in the TP53 gene [22]. Patients with Li-Fraumeni syndrome have an increased risk for developing cancers including brain tumors [22]. Germline TP53 mutations have been observed more frequently in patients who present with multifocal gliomas, glioma and another primary malignancy, or glioma associated with a family history of cancer than in patients with other brain tumors [23]. The VHL syndrome is an autosomal dominant disorder associated with a mutation in the VHL tumor suppressor. The resulting mutation leads to hemangioblastomas, pancreatic cysts and neuroendocrine tumors, renal tumors, and pheochromocytomas [24]. Lastly, increased incidence of gliomas within families has been documented in several reports [25-27]. An estimated 5% of all glioma cases may be familial [28]. However, the pattern of glioma occurrence in many families suggests environmental causes rather than a predisposing hereditary disease [29].

Clinical Presentation

Patients with primary brain tumors can present with generalized or focal signs and symptoms [30]. Typically, generalized symptoms occur later in the disease pathogenesis as the tumor grows and causes increased intracranial pressure leading to headache, seizure, nausea, vomiting, and altered mental function [30]. Focal symptoms such as focal neurological deficit (e.g., hemiparesis and aphasia) are attributed to low-grade or high-grade tumors and reflect the intracranial location of the tumor. Roughly 77% of all patients with primary brain tumors report a dull tension-type headache [31] that can persist for more than six months in 50% of patients [4]. Although headache is the most common initial presenting symptom [32,33], other symptoms are often associated with headaches including seizures in 50% of patients, visual disturbances in 40% of patients, and nausea and vomiting in 38% of patients [31].

Seizures are common in patients with brain tumors with 15-95% of patients presenting with at least one seizure during the course of their illness [34]. Patients with low-grade gliomas present with seizures more frequently (65-95%) than patients with GBMs (15-25%). In one large study, 23% of patients had experienced at least one seizure before tumor diagnosis [35]. Eighteen percent of patients with GBM initially presented with seizures [32,33]. Patient age, tumor location and histology are associated with seizure occurrence. Patients aged 30-50 years experienced seizures more frequently [35]. Tumor involvement of the frontal, frontoparietal, temporal, and frontotemporal lobes were more often accompanied with seizures [35]. Finally, based on histological diagnosis, patients with mixed gliomas, oligodendrogliomas, and astrocytomas experienced seizures at 62%, 53%, and 42%, respectively [35].

Imaging

The scope of neuroradiology tumor imaging has continued to evolve. Within the past decade we have seen imaging move from indirect diagnosis of lesion using cerebral angiography to precise lesion diagnosis with multi planar CT and MRI. Continued advancements have furthered the imaging role to include not only precise lesion localization and diagnosis but also surveillance of treatment response and lesion recurrence. A comparison of CT to MRI reflects that while CT has many advantages (faster, cheaper and more readily available) MRI remains the modality of choice given its superior soft tissue contrast resolution [36].

Institutional MRI brain tumor protocols may vary slightly but most will include the following conventional sequences: T1 pre and post-
contrast, T2, FLAIR, Gradient Recall Echo (GRE) and Diffusion Weighted Imaging (DWI) [36]. T2 and FLAIR are fluid weighted sequences helping to identify tumoral cystic changes, necrosis, as well as cytotoxic and vasogenic edema. The DWI sequence can reveal elevated nuclear to cytoplasmic ratios. GRE capitalizes on the intrinsic artifact of magnetic substances to reveal the presence of hemorrhage or calcification even at a microscopic level. T1 pre and post contrast imaging assesses the integrity of the blood brain barrier. Cumulatively, a lesion’s conventional MRI characteristics not only help in diagnosis but also in assessing tumor histological grade.

As the complexities of tumor genesis are discovered, new treatment regimes will be designed. Unfortunately, these new therapies can result in unpredictable and often confusing imaging appearances on conventional MRI sequences. Specifically with GBM therapies the phenomena coined pseudo progression and pseudo response have emerged [37]. These, as well as long known phenomena of radiation necrosis, are often indistinguishable from tumor progression on routine conventional MRI sequences. While serial follow-up imaging remains the general standard for identification of recurrent tumor and/or its progression, new and old advanced imaging techniques are being applied to help define treatment effects versus recurrent tumor. Primary amongst these are Dynamic Susceptibility Contrast (DSC) Perfusion, Permeability, and Spectroscopy.

Perfusion helps define degrees of angiogenesis by measuring the relative cerebral blood volume; Permeability can assess the leakiness of microscopic junctions; and Spectroscopy can reveal a lesion’s molecular composition. Variable success has been observed with these modalities and a rising school of thought is to assess the tumor both pre and post therapy not only to have a baseline of a lesion's behavior, but also to help define a lesion's grade and therefore guide appropriate therapy decisions.

The following is an example of a GBM post resection with a large region of enhancement (Figure 1A) and vasogenic edema (Figure 1B) developing rapidly post resection. Advanced DSC perfusion identified lack of elevated blood volume compatible with pseudo progression (Figure 1C), which was confirmed post biopsy.

Figure 1: Imaging of GBM tumor post resection. (A) T1-weighted magnetic resonance image (MRI) showing enhancement. (B) Fluid-attenuated inversion recovery (FLAIR) image showing vasogenic edema. (C) Dynamic Susceptibility Contrast perfusion MRI showing lack of elevated blood volume within enhancing region.

Separate imaging advancements include Diffusion Tensor Imaging (DTI) with tractography and functional MRI. Although these imaging techniques are not primarily used as a diagnostic tool, they can localize a lesion precisely and define the specific affected tracks and their function [38]. This can be invaluable in guiding lesion resection and prediction of post resection functional prognosis.

Finally, the development of 3D steady state volumetric imaging has led to faster and thinner imaging than ever before. A technique which incompletely fills ‘K’ space trades an increase in imaging speed for lesser degrees of soft tissue contrast. However, the gain in spatial resolution is profound and logical paring of this with navigational software has become routine for intra-operative stereo-tactic lesion resection.

The extent of surgical resection is an important prognostic factor in neurooncology and the goal of image-guided surgical resection is to help achieve maximum safe resection [39]. Three approaches fall within the image-guided resection modality and include intraoperative MRI (iMRI) and neuronavigation, fluorescent imaging, and intra-operative brain mapping. Intraoperative MRI allows for real-time visualization of complex three-dimensional structures of the brain to help guide the removal of brain tumors. In addition to using intra-operative structural MRI, recent efforts have been made to integration other MRI modalities, including iMRI and DTI, into neuronavigation systems [40]. This unique integration allows surgeons to account for brain shift and other anatomical changes that often affect maximal tumor debulking, particularly in eloquent areas of the brain. In addition, image quality of intra-operative ultrasound is now comparable to intra-operative MRI and is being integrated into neuronavigation systems to enable acquisition of 3D ultrasound data for direct image guidance [40,41].

Surgical approaches that can complement iMRI and help surgeons visually distinguish neoplastic tissue from healthy tissue may facilitate maximum safe resection while minimizing the amount of residual tumor cells [42].

Although several types of contrast agents are currently being developed for intraoperative surgical oncology, only a small number have been FDA approved [43]. These include several passive contrast molecules including methylene blue, Indocyanine Green (ICG), and sodium fluorescein. ICG is a water-soluble probe that binds human serum albumin and is used to visualize solid tumors [44]. ICG has proven useful in brain tumor resections as it was used intraoperatively to identify tumor boundaries in glioma surgery [45]. Fluorescein is a fluorophore that can cross capillaries and provide fluoresce in the extracellular matrix [46]. Due to this property, Fluorescein is useful in identifying infiltrative tumor margins [47].

5-Aminolevulinic acid (5-ALA) is another contrast agent that is converted to an active fluorescent state in situ. In a phase III trial, surgical resection with 5-ALA demonstrated a 1.5 month increase in progression-free survival compared to patients treated with surgical resection using white light (5.1 months vs. 3.6 months) [48].

Several studies have investigated combining structural imaging with functional imaging to study brain connectivity [49,50]. This approach is useful in understanding brain function organization. Therefore, brain mapping in eloquent regions of the brain is vital for maximum resection while at the same time preserving quality of life. The current gold standard for brain mapping is cortical and Subcortical Electrical Stimulation (CSES). However, with advances in functional imagining, the utility of fMRI and DTI-FT is being evaluated for cortical mapping. When compared to CSES, the sensitivity of fMRI in detecting sensorimotor areas ranges from 82% to 100% [51-54]. Yet, the utility of fMRI diminishes for language areas [52]. Evaluation of DTI-FT is also complicated and no clear conclusions can be drawn [52]. While we make strides in brain mapping using functional imaging, the use of CSES has allowed us to treat patients once deemed unsuitable for

surgery. CSES demonstrates high sensitivity with the ability to map the entire exposed cortical region. Also, CSES provides excellent prognosis with removal of negative cortical and subcortical areas leading to no permanent neurological impairment [55].

**Neuroepithelial tumors**

Although the WHO classifies neuroepithelial tumors into nine major groups, this review will only focus on the most frequent types including astrocytic, oligodendroglial, ependymal and mixed. We will also discuss the most common malignant neuroepithelial tumor in children, medulloblastomas.

**Astrocytic Neoplasms**

Glial-appearing cells give rise to most primary CNS neoplasms (gliomas). Of these, astrocytomas are the most common. Astrocytomas, anaplastic astrocytomas, and glioblastomas are termed astrocytic neoplasms.

Astrocytomas have a propensity for progression with 50%-75% of astrocytomas progressing to anaplastic astrocytomas or GBMs [57]. Therefore, all patients with astrocytomas need regular followup. GBM has the highest incidence of any primary neuroepithelial neoplasm, accounting for approximately 50% of intracranial gliomas [58].

**Histology**

**Pilocytic astrocytoma (WHO grade I)**

**Macroscopically:** Tumors are often cystic with discrete borders.

**Microscopically:** Neoplastic cells are usually bipolar with elongated hairlike processes that are arranged in a parallel fashion. Rosenthal fibers, which are tapered corkscrew shaped eosinophilic hyaline masses, are often present.

**Diffuse Astrocytoma (WHO grade II)**

**Macroscopically:** Cerebral astrocytomas diffusely expand beyond the white matter boundary oftentimes distorting the overlying gray matter. The neoplastic process is poorly demarcated.

**Microscopically:** Neoplastic cells show mild atypia. Fibrillary astrocytomas may appear as bare nuclei. Astrocytomas show varying degrees of astrocytic differentiation. They may exhibit prominent fibrillary strands of eosinophilic cytoplasm, or plump cell bodies in which the nucleus is displaced by homogeneous eosinophilic cytoplasm, oftentimes referred to as the gemistocytic phenotype.

**Anaplastic Astrocytoma (WHO grade III)**

**Macroscopically:** Anaplastic transformation may be associated with little macroscopic change from astrocytomas. Although on MRI, areas undergoing anaplastic progression often show contrast enhancement.

**Microscopically:** Cytological and nuclear pleomorphism may be more pronounced. Nuclear to cytoplasm ratio is increased. Mitotic activity distinguishes the anaplastic astrocytoma from diffuse astrocytoma variants. However, necrosis is not present.

**GBM (WHO grade IV)**

**Macroscopically:** GBM distorts the normal anatomy of the brain. Foci of cyst formation, necrosis and hemorrhage are mixed with mucoid gray neoplastic tissue. GBMs commonly appear as spherical masses with a necrotic center, which may be seen on MRI as a ring enhancing mass. Their growth is not restricted to one hemisphere as they often track along the corpus callosum affecting the contralateral hemisphere, commonly referred to as a butterfly glioma. GBMs may also spread along CSF pathways.

**Microscopically:** Necrosis and a florid microvascular proliferation are the key features separating GBM from the two other diffuse astrocytic neoplasms. Thrombi are often found in these vessels and are responsible for the foci of necrosis. Cellular pleomorphism is more extreme than in anaplastic astrocytomas. Finally, palisading of cells around necrotic areas is often seen.

**Molecular Genetics**

Although many important genetic alterations have been known in gliomas, new technologies have shed light onto novel discoveries in recent years. These genetic alterations are currently being used as biomarkers. A biomarker is a genetic or biochemical feature that can be assessed to indicate a particular diagnosis, prognosis, or response to treatment. As technology advances along with our understanding of the complex molecular genetics underlying brain tumors, the number of biomarkers will likely increase.

**O6-methylguanine methyltransferase (MGMT) promoter methylation:** MGMT is a DNA repair protein that repairs the chemotherapy-induced alkylation at the O-position of guanine, the essential mediator of alkylating drug cytotoxicity, and thus counteracts the effects of alkylating chemotherapeutic drugs such as nitrosoureas or temozolomide. Hypermethylation of the MGMT gene promoter is one mechanism to silence the gene and thus reduce the protein concentration. As such, hypermethylation of MGMT is associated with 20-40% of patients with GBM [59]. Several clinical trials and cohort studies have shown that the MGMT promoter methylation phenotype is associated with prolonged progression-free and overall survival in patients with GBM who are being treated with alkylating class of chemotherapy drugs [60-62]. In a randomized clinical trial assessing radiotherapy alone with radiotherapy combined with concomitant and adjuvant treatment with temozolomide in newly diagnosed patients with glioblastoma, the benefit from chemotherapy was almost exclusively attributable to patients with tumors with a methylated MGMT gene promoter [62]. In the same study, patients with a methylated MGMT promoter showed better overall survival than patient with an unmethylated MGMT promoter [62]. These results suggest that treatment strategies should be individualized dependent on MGMT status and that MGMT status has prognostic value.

**Loss of chromosomes 1p and 19q:** The combined loss of chromosomal arms 1p and 19q is a cytogenetic aberration resulting from an unbalanced t(1;19)(q10;p10) translocation occurring in 50%-90% of oligodendrogliomas and 30%-50% of oligoastrocytomas [63]. Tumors with the 1p/19q deletion respond better to chemotherapy and radiotherapy resulting in prolonged progression free survival and overall survival in patients, especially with anaplastic oligodendrogliomas [64,65]. Outside of oligodendrogliomas, 1p/19q codeletions are rare and additional studies are necessary to determine whether these tumors have a less aggressive natural course [66].
Isocitrate dehydrogenase (IDH) mutation: Single point mutations in the metabolic genes IDH 1 and 2 were recently discovered in gliomas [67,68]. Approximately 80% of grade 2 and grade 3 gliomas as well as secondary GBMs harbor a single amino acid missense mutation in IDH1 at arginine 132 [69]. The IDH2 mutation at arginine 172 is less common and is mutually exclusive with mutations in IDH1 [69]. IDH1 and 2 mutations promote a neomorphic reaction in which the normal product α-ketoglutarate is converted to 2-hydroxyglutarate (2-HG) (a candidate oncometabolite) in a reaction that consumes, rather than produces, NADPH [70]. The accumulation of high concentrations of 2-HG has been shown to contribute to the formation and malignant progression of gliomas [70]. In addition, the IDH1 mutation has been associated with the CpG island methylator phenotype (G-CIMP) in gliomas, which is associated with younger patients, improved survival, and is more common in low and intermediate grade gliomas [71,72].

Epidermal Growth Factor Receptor (EGFR) variant III: EGFR is a cell surface receptor involved in the control of cell proliferation. A common alteration of the EGFR locus observed in gliomas is a genomic rearrangement with amplification of EGFR resulting in an in-frame deletion of exons 2-7 from the extracellular domain, causing a truncated mutant receptor known as EGFR variant III (EGFRVIII) [73]. This truncated mutant receptor is therefore ligand-independent and constitutively active which confers enhanced tumorigenicity on glioma cells by increasing proliferation and reducing apotosis [74]. Overexpression of EGFR is observed in 50%–60% of GBMs with the most common EGFR mutation (EGFRVIII) expressed in 24%–67% of cases [75-79]. Since the EGFRVIII mutation creates a new surface epitope, vaccination strategies based on this unique peptide sequence demonstrated promising results, thus warranting phase 3 trials [80,81]. The prognostic relevance of EGFR overexpression and EGFRVIII is unclear, but long-term survival might be worse in patients whose tumors carry the EGFRVIII mutation than in those who do not [75,82].

BRAF fusion or point mutation: The BRAF gene encodes a protein called B-Raf that is involved in cell signaling that promotes cell growth. Tandem duplications of BRAF and KIAA15A9 results in a gene fusion product called KIAA15A9-BRAF, which has constitutive B-Raf kinase activity. This fusion event is frequently detected in pilocytic astrocytomas, pleomorphic xanthoastrocytomas, and malignant astrocytomas [14,40]. The detection of the KIAA15A9-BRAF fusion is often used to help distinguish pilocytic astrocytomas from higher-grade astrocytic tumors. Other BRAF gene alterations including activating point mutations in BRAF (e.g., BRAFV600E) have also been identified in low-grade as well as higher grade (III/IV) gliomas [83,84]. Small-molecule BRAF kinase inhibitors, such as CCT239065 and RG7294, have been evaluated in melanomas and may provide a new therapeutic approach to treat brain tumors harboring BRAF mutations [85].

Recent advances in sequencing along with the vast data from The Cancer Genome Atlas have re-classified GBMs into four distinct genetic subtypes including classical, mesenchymal, proneural, and neural [86].

Classical: The classical subtype features many of the common gene alterations observed in GBMs including chromosome 7 amplifications and chromosome 10 deletions. In addition, EGFR amplification was observed more frequently in classical GBMs than the other subtypes [86]. Other common abnormalities in genes, TP53, NFI, PDGFRA, or IDH1 are not found in this group [86]. In response to aggressive treatment, patients in the classical group lived the longest compared to those in the other groups [86].

Mesenchymal: The mesenchymal subtype features mutations in the NF1 gene including focal hemizygous deletions of the 17q11.2 region, which contains the NF1 gene [86]. Mutations in the PTEN and TP53 tumor suppressor genes are also frequently observed in this subtype [86]. Interestingly, tumors of the mesenchymal subtype express Schwann cell markers such as the family S100A as well as microglial markers [86]. Genes associated with inflammation are enriched in this subgroup, which is evident in the observation that there is a higher overall fraction of necrosis in these tumors [86]. Patients in this subtype typically survive longer after aggressive treatment than those in the proneural and neural groups [86].

Proneural: The proneural subtype features alterations of the PDGFRA gene and point mutations in the IDH1 gene [86]. Although focal amplifications of the PDGFRA locus are seen in all GBM subtypes, proneural tumors have the highest rate. TP53 mutations and loss of heterozygosity are frequently observed in this subtype, while chromosome 7 amplification and chromosome 10 deletion are less prevalent [86]. This subtype shows high expression of oligodendrocytic development genes (e.g., PDGFRA, NKKX2-2 and OLIG2), which may help explain its atypical GBM subtype status [87]. In addition, the proneural subtype contains several proneural development genes such as SOX, DCX, DLL2, ASCL1, and TCF4 [88]. This subgroup consistently represents younger patients than the other subgroups and is often associated with secondary GBMs [86]. Interestingly, patients in the proneural group who received aggressive treatment did not have a significant survival advantage compared with patients in the proneural group who did not receive aggressive treatment [86].

Neural: The neural subtype features expression of neuron markers such as NEFL, GABRA1, STY1, and SLC12A5 [86]. Tumors of this subtype are associated with neural, astrocytic and oligodendrocytic gene signatures [86]. Patients in the neural group had some improvement in survival but not as significant as those patients in the classical and mesenchymal groups [86].

Treatment and Prognosis

Although pilocytic astrocytomas commonly arise in the first two decades of life, late presentation in adults is reported and typically has a less favorable outcome [89]. If there is a high level of suspicion at the time of presentation for pilocytic astrocytoma, decision-making should consider the following: obtaining tissue diagnosis, restoring cerebrospinal fluid flow and decompressing adjacent neural structures, and non-surgical alternatives when an invasive procedure is precluded or incomplete.

Gross total resection of pilocytic astrocytomas provides the greatest clinical outcomes [90]. When risk of surgery is too high or if gross total resection cannot be performed, consideration for radio- and chemotherapy can be given. The long-term risks of radiotherapy in children suggest it be employed only in cases of recurrence or pilocytic astrocytomas with aggressive nature. While various case series have found prolonged survival after radiation therapy in children [91-93], the rate of recurrence after 5 years remains high. In a 10-year prospective trial where practitioners felt irradiation posed a high-risk for neurocognitive injury, a carboplatin and vincristine (CV) regimen was compared to a thioguanine, procarbazine, lomustine, and vincristine (TPCV) regimen. Although five-year event-free survival appeared more favorable using TPCV, toxicity observed with both...
regimens presented a major limitation for long-term effectiveness in either group [94].

A multimodality approach consisting of surgical resection, radiation therapy, and chemotherapy is used in the treatment of malignant gliomas. Surgery plays a key role in the treatment of malignant gliomas as it allows for both cytoreduction and confirmation of diagnosis. Furthermore, there is growing evidence in the literature that achieving gross total resection is important in prolonging survival [95,96]. As discussed in the imaging section, advances in neuroimaging and brain mapping has allowed for increased gross total resection.

Radiation therapy is currently recommended for all patients with grade III and IV gliomas (anaplastic astrocytomas and GBM, respectively). Only infants, young moribund children, and patients declining treatment in favor of supportive care would not be recommended to receive some form of radiation therapy shortly after diagnosis. Radiation therapy alone has been shown to improve median survival from 3-4 months to 9-12 months [97,98]. Although radiation therapy has shown a clear improvement in survival for patients with primary GBMs, radiotherapy for recurrent GBMs is controversial mainly due to the serious risks associated with reirradiation including necrosis of healthy brain tissue [99]. Despite these serious risks, studies suggest there may be a benefit to a more focused radiation therapy through the use of stereotactic radiosurgery or fractionated stereotactic reirradiation [100,101].

Alkylating agents are the most frequently used chemotherapy drugs in treating anaplastic astrocytomas and GBMs. The cytotoxic effects are mediated primarily through DNA cross-linking, leading to cell death by apoptosis. Carmustine (BCNU) has been shown to prolong survival of GBM patients in two clinical trials [102,103], however, due to the post-operative complications; the addition of BCNU to a patient's treatment protocol is unclear and ultimately determined by the treating physician. In 2005, temozolomide was shown to improve median survival and increase the likelihood of long-term survival with newly diagnosed GBM when given concurrently with RT and then following RT [98]. Since this publication, the Strupp protocol, involving surgery followed by radiotherapy plus concomitant and adjuvant temozolomide for the treatment of malignant gliomas is the current gold standard [98].

Additional chemotherapeutic agents targeting specific molecules currently used in treating malignant gliomas include inhibitors of Epidermal Growth Factor Receptor (EGFR), Platelet-Derived Growth Factor Receptor (PDGFR), Vascular Endothelial Growth Factor (VEGFR), mammalian Target of Rapamycin (mTOR), Protein Kinase C (PKC), RAF-MEK-ERK pathway, and integrins [104]. With new chemotherapeutic agents being developed the gold standard for evaluating these agents remain randomized clinical trials. Recently, an anti-VEGF monoclonal antibody, bevacizumab, was evaluated in two randomized phase 3 clinical trials in which it was concluded that although there was improved progression-free survival, the overall survival in patients was not improved [105,106]. Although overall survival was not improved in these studies, progression-free survival increased 3-4 months and bevacizumab may still hold promise as an option for treating GBMs. With the development of novel chemotherapeutic agents, a combined multimodality approach including both chemotherapy and radiotherapy is needed to overcome tumor resistance through the use of multi-targeted strategies.

Since survival for patients with GBMs is relatively short, identifying prognostic indicators in order to stratify patients into risk groups may provide valuable in determining the best therapeutic approach including enrollment into active clinical trials. Lamborn and colleagues surveyed 832 GBM patients enrolled into prospective clinical trials in order to identify potential risk groups [107]. From their analysis, they identified four risk groups in which the two lower risk groups included patients under the age of 40 with the lowest overall risk group being young patients with frontal lobe tumors only [107]. The intermediate risk group included patients aged 40-65 with KPS >70 who underwent subtotal or total resection of the tumor. Finally, the highest risk group included patients over the age of 65 or patients aged 40-65 with either KPS <80 or who only underwent biopsy [107].

In addition to the age of the patient and the KPS score, other clinical parameters serve as prognostic indicators of long-term survival. Tumor size and location are also important indicators as extent of resection is dictated not only by tumor size but also by location of the tumor. Finally, grade of tumor is an important indicator of long term survival as the higher the grade the more malignant the tumor is, which directly results in a poorer prognosis.

**Oligodendrogliomas**

Historically, oligodendrogliomas (ODG) were thought to account for only about 4% of primary brain tumors [108], however, with better understanding of the tumor biology, it is thought that ODG may comprise as much as 25-33% of gliomas [109,110]. Up to 57-87% of patients with ODGs present with seizures [108,111] with 22% of patients presenting with headaches [108].

**Histology**

Calcifications are typically seen histologically with 73% of tumors having microscopic calcifications [112]. Histopathologic analysis of these tumors demonstrates a lucent perinuclear halo typically referred to as a “fried egg” appearance along with a “chicken-wire” vascular pattern [110]. Although these features are common to ODG, they are not pathognomonic. Since most ODGs contain microtubules and not glial filaments, they typically do not stain for Glial Fibrillary Acidic Protein (GFAP) [113]. Attempts for a grading system has been met with controversy, mainly surrounding the lack of prognostic significance [114]. Therefore, for prognostic reasons, a two classification system has been proposed that includes low grade; oligodendroglioma (WHO grade II) and high grade; anaplastic oligodendroglioma (WHO grade III) [114,115].

**Treatment and Prognosis**

Surgery is mainly reserved for low grade ODGs, while surgical data for high grade ODGs is less convincing. Radiation therapy for ODGs is also unclear [116] with one retrospective study showing a 10-year survival rate of 56% in those patients receiving postoperative radiation >45 Gy [117], while in another study, no difference in 5-year survival was observed in patients with or without postoperative radiation [118]. Chemotherapy is therefore the primary modality for treating ODGs as most respond to chemotherapy [119]. The 10-year survival rate for ODGs is 10-30% with pure ODGs having a higher survival rate than mixed ODGs [108,112]. The presence of calcifications on imaging as a prognostic indicator was evaluated in one series, however, additional studies are needed before conclusions can be drawn [108]. Finally, chromosomal 1p and 19q loss is associated with longer survival rates [120].
Ependymomas

Ependymomas are a rare type of glial tumor that is believed to arise from ependymal cells lining the cerebral ventricles and along the central canal of the spinal cord. A large portion of intracranial ependymomas (36-60%) occur in children, making ependymomas the second most common malignant brain tumor in this population [121]. Spinal ependymomas are more common in adults, occurring in 96% of cases [122].

Classification

Ependymomas are usually well circumscribed and benign but they have been known to be invasive. Ependymomas are divided into four major subgroups including myxopapillary (WHO grade I), subependymoma (WHO grade I), classic ependymoma (WHO grade II), and anaplastic ependymomas (WHO grade III). Within classic ependymomas there are an additional four variants including cellular, papillary, clear cell, and tanyctye. Lastly, it is worth noting that once considered a variant, ependymoblastoma, is now being regarded as a rare childhood primitive neuroectodermal tumor with abundant mitotic figures and true rosettes [123].

Histology

Similar to all brain tumors, the diagnosis of ependymoma requires histological confirmation. Classical ependymomas are characterized by dark small nuclei. They also show two cytoplasmic patterns: perivascular pseudorosettes and true rosettes. Perivascular pseudorosettes are areas of radiating neoplastic cells that lack nuclei and surround blood vessels. True rosettes are areas of ependymal tubules around a central blood vessel.

Treatment and Prognosis

Since ependymomas are highly radiosensitive, the best approach for treatment of ependymomas is gross total resection followed by radiation therapy. The role of chemotherapy for the treatment of ependymomas is currently unclear [124].

Mixed gliomas

Mixed gliomas are tumors that contain both oligodendroglioma and astrocytoma cells. These tumors can be classically divided into oligoastrocytoma (WHO grade II) and anaplastic oligoastrocytoma (WHO grade III). Oligoastrocytomas comprise 10-19% of low-grade gliomas and usually develops in middle-aged adults [125]. Treatment is usually surgical resection. If however, these tumors recur, the treatment approach is surgery followed by radiotherapy and chemotherapy.

Medulloblastoma

Medulloblastomas are the second most frequent childhood brain tumor after Pilocytic astrocytomas, and the most common malignant brain tumor in children comprising roughly 25% of intracranial tumors [126]. They occur exclusively in the posterior fossa with a peak incidence between 4 and 7 years [127]. Patients with medulloblastomas often present with symptoms of increased intracranial pressure (hydrocephalus) [128]. Since these tumors grow in the posterior fossa, gait ataxia, truncal instability, vomiting, dizziness and vision problems are also common symptoms caused by involvement of the cerebellum, brainstem, or cranial nerves. Since metastases along the cranio-spinal axis are present in roughly 33% of patients [126], evaluation for metastases is recommended.

Classification and Histology

Although all medulloblastomas are classified as WHO grade IV, within this classification scheme, there are currently five variants including classic, desmoplastic/nodular, Medulloblastoma with Extensive Nodularity (MBEN), Large Cell (LC), and Anaplastic Medulloblastoma [129].

**Molecular pathways:** While the etiology is unknown, roughly 2-5% of medulloblastomas are associated with nevoid basal cell carcinoma syndrome (Gorlin syndrome), which is caused by mutations in the patched-1 gene (PTCH-1), and familial adenomatous polyposis, which is caused by inactivating mutations in the adenomatous polyposis coli gene [130,131]. In addition, great strides have been made in our understanding of the oncogenesis of medulloblastomas. Based on gene expression profiles using tissue microarrays and substantiated using whole genome and whole exome sequencing, medulloblastomas have been separated into four distinct subgroups based on their unique molecular profiles [132-135]. These groups include sonic hedgehog (SHH), wingless (WNT), group 3, and group 4.

**SHH medulloblastomas:** This subgroup comprises roughly 25-30% of medulloblastomas and is characterized by high desmplasia [132,134-137]. The overexpression of SHH pathway leads to the binding and inactivation of PTCH-1, which normally blocks activation of a number of transcription factors through the inhibition of smoothened (SMO). SHH also upregulates MYCN, which is involved in the cell cycle. In addition to mutations in PTCH-1, mutations in SMO and Suppressor of Fused Homolog (SUFU) have also been observed in SHH medulloblastomas [138,139]. Chromosomal aberrations have also been associated with this subgroup including loss of 9q (accounting for 21-47%), 10q, 20p, 21p and gain of chromosome 3q and 9p [132,136,140]. The majority of SHH medulloblastomas occur in infants under the age of 3 and again in adults above age 16 [136,141]. In fact, nearly half of all adult medulloblastomas are of the SHH variant [142]. The overall survival is good in infants and intermediate in adults [143].

**WNT medulloblastomas:** The WNT medulloblastoma subgroup harbors mutations in essential genes of the WNT pathway including APC, β-catenin, and axin 1. Roughly 10-15% of medulloblastomas fall within this subgroup [137]. They are characterized by classic histology, more than 90% of WNT tumors, affecting patients above 3 years old, good prognosis, and infrequent metastasis [137]. Unlike SHH tumors, WNT tumors rarely affect infants and the overall survival is generally good [141,143].

**Group 3 and 4 medulloblastomas:** Both of these subgroups present with common clinical features and share similar molecular profiles. The age of onset for both groups vary with Group 3 peaking in childhood (3-10 years), while Group 4 has a more distributed age of onset from infancy to adulthood [136,141]. The majority of tumors in both groups display classical histology. Chromosomal aberrations are common to both groups with isochromosome 17q representing the most frequent structural alteration [135]. Gain of 7 and 18q along with loss of 8 and 11p are also common abnormalities [136,137,147]. MYC amplification in group 3 is the main difference between these groups since MYC amplification is rarely observed in group 4 [147,148]. Conversely, enrichment of chromosome X loss is more common in
group 4 as observed in 80% of females in this group [147]. Lastly, both groups have similar metastatic rates but group 3 has a poorer prognosis than group 4, which shows intermediate prognosis [148].

**Treatment**

Medulloblastomas are among the most radiosensitive tumors of the central nervous system and are moderately chemosensitive. Therefore, the recommended therapeutic approach is surgical debulking followed by radiation therapy. 36 Gy to the entire craniospinal axis with a boost therapy dosage [149]. Medulloblastomas are moderately chemosensitive, and as such, chemotherapy is now an integral part of the treatment of these tumors, including recurrent disease [150]. Some chemotherapy agents used include lomustin, cisplatin and vincristine. Finally, placement of permanent ventriculoperitoneal shunts is required in 30-40% of patients after tumor resection of the posterior fossa [151,152].

**Prognosis**

Patients with medulloblastomas are classified into three risk groups that help facilitate treatment and provide predictions on prognosis. These groups include standard risk, intermediate risk, and poor risk. Patients with no residual tumor demonstrated on post-operative MRI along with negative CSF results are classified as standard risk and carry a 5-year survival rate of 73% [153]. Residual tumor measuring greater than 1.5 cm2 on post-operative MRI and presence of tumor cells in the brain, spine, or CSF are characteristic of patients in the poor risk group. These patients have a poor prognosis with a 5-year disease free survival of 36-52% [154]. The intermediate risk group is poorly characterized leaving the other two groups as primary predictors. Interestingly, females have a better prognosis than males [155].

**Meningioma**

Meningiomas arise from the layer of tissue covering the brain and spinal cord. Meningiomas are the most common benign intracranial tumor accounting for about 13-26% of all primary brain tumors [156]. Most meningiomas are intracranial, however, spinal meningiomas may occur accounting for an estimated 7.5 to 12.7% of all meningiomas [157]. The vast majority of meningiomas rarely metastasize with a rate of less than 1 in every 1,000 meningiomas [158]. The most common sites of metastasis include lung and pleura, liver, lymph nodes, and bone [159]. Due to the slow growing nature of meningiomas, most remain asymptomatic. Meningiomas rarely affect children with an incidence rate of roughly 2.2% [160] and of these, prevalence of neurofibromatosis was 14.5% [161]. There have been reports documenting prevalence of meningiomas in roughly 50% of NF2 patients [162] with one study reporting prevalence as high as 58% [163]. If multiple meningiomas are observed, suspicion of neurofibromatosis type 2 is high. Both neurofibromatosis types 1 and 2 will be discussed in the vestibular schwannoma section.

**Classification and Histology**

Meningiomas have a complex and broad range of histological patterns. The WHO currently recognizes 16 different variants grouped into three grade designations (Table 1) [129]. Meningiomas falling in the WHO grade I classification include: meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and metaplastic. Although each subtype has a distinct histological pattern, all WHO grade I meningiomas have a low recurrence rate of 9% with no evidence of brain invasion [164]. Three subtypes of meningiomas fall within WHO grade II and these include: chordoid, clear cell, and atypical. One major difference between the 2000 WHO classification scheme and the recent 2007 WHO classification scheme is the recognition that meningiomas with evidence of brain invasion should be classified as WHO grade II regardless of a benign histological appearance [165,166]. WHO grade II meningiomas have a recurrence at of 29% [164]. Lastly, meningiomas in the WHO grade III group include papillary, rhabdoid, and anaplastic with the anaplastic variant representing the majority of WHO grade III cases [129]. All WHO grade III meningiomas have increased mitotic activity with a recurrence rate of 50% [164].

**Treatment**

If the tumor is not causing symptoms, tumor growth may be watched using serial MRIs. Otherwise, surgery is the standard of care for treating meningiomas. Similar to other tumor types, extent of tumor resection is beneficial for minimizing the risk of tumor recurrence. As a result, in 1957, Simpson established a classification system consisting of five subdivisions to assess extent of resection of meningiomas and to correlate postoperative recurrence rates with extent of resection [167]. In his grading system, Simpson grade I is defined as complete tumor resection with excision of the dural attachment and any abnormal bone. If the venous sinus is involved, complete resection of the sinus is also performed. Simpson grade II is defined as complete tumor resection with coagulation of the dural attachment. Simpson grade III is defined as complete tumor resection without resection or coagulation of the dural attachment. Simpson grade IV is defined as a subtotal resection. Finally Simpson grade V is defined as a simple decompression, with or without biopsy. The risk of tumor recurrence (minimum of 6 months of follow-up) for Simpson grades I, II, III, and IV were 9%, 16%, 29%, and 39%, respectively [167].

With advancements in surgical techniques and treatment options, such as radiation therapy, relying solely on the Simpson grading system of meningiomas in the modern era to predict recurrence is inconclusive. Therefore, cell proliferation markers, such as Ki-67 (MIB-1 – monoclonal antibody) are being evaluated to complement the Simpson grading system in predicting tumor recurrence [168]. In a study conducted by Oya and colleagues, they determined that the MIB-1 index could differentiate meningiomas with a high risk of recurrence [168]. Further, the authors conclude that using the MIB-1 index could be beneficial in planning optimal follow-up strategies with a shift from attempting aggressive resection to valuing the quality of the patient's life [168].

Several retrospective studies have demonstrated that radiation therapy (e.g., external beam radiation therapy and stereotactic radiosurgery) can provide improved and durable local control in selected patients with meningioma [169]. For WHO Grade I or presumed Grade I meningiomas, radiation therapy achieved long-term local control in 68% to 100% of cases at 5 to 10 years, including patients treated postoperatively, primarily, or following tumor recurrence. The use of stereotactic radiosurgery is considered most effective for patients with small meningiomas (usually less than 3 cm in diameter or 10 cm3 in volume), those with distinct margins, and those at sufficient distance from functionally important brain, nerves, and other critical structures to permit safe delivery of an adequate target dose [169].
For high-grade meningiomas, a multimodal approach using radiation therapy and/or chemotherapy is usually given. Achieving maximum resection and adjuvant radiotherapy have been shown to be independent predictors of patient survival and disease-free survival in the treatment of malignant meningioma [170]. Evaluating stereotactic radiosurgery in the setting of subtotal resection or recurrence, reported local control rates (>2 years) range from 0% to 90%, with the majority falling within 50% to 80% for WHO grade II meningiomas [169]. While some studies have suggested stereotactic radiosurgery is not indicated for malignant meningiomas [171], others have shown improved local control rates of 17% at 15 months [172]. Finally, for recurrent atypical or anaplastic meningiomas not suitable for radiosurgery, resection followed by permanent brachytherapy is a potential salvage therapy that has shown promise in the clinical setting [173,174]. In the largest series (n=21) to date examining brachytherapy for therapy for the recurrence of aggressive atypical and anaplastic meningiomas, Ware et al. reported a median survival of 1.6 years after [125] 1 implantation for atypical meningiomas and 2.4 years for anaplastic meningiomas [173]. Due to the high complication rates observed including radiation necrosis occurring in 27% in one study, meticulous surgical technique and medical therapies to assist with wound healing after surgery is required [173].

For meningiomas that are inoperable and/or radiation-refractory, chemotherapy is often used with little to no effect. As a result of failed chemotherapeutic approaches, several studies have investigated various chemotherapies in which all have been disappointing [175,176]. Although there is limited data, hydroxyurea, somatostatin analogues and interferon-α have all been modestly successful in patients with recurrent meningiomas [175]. Further, emerging targeted therapies including sunitinib, may prove useful in refractory meningiomas [175,176].

Prognosis

Prognosis for patients with benign meningiomas is generally good with a 5-year survival rate of 91.3% [177]. Recurrence depends on extent of surgical resection with a recurrence rate of 8% in cases with a gross total resection, a 29% in cases with a subtotal resection [178]. Atypical meningiomas have been reported to have a higher rate of local recurrence and are associated with lower survival rates compared to benign meningiomas [179]. Similar to benign meningiomas, achieving a gross total resection of atypical meningiomas was associated with a lower recurrence rate (11%) compared to achieving a subtotal resection (100%) [179]. A similar trend of increased survival is also associated with (grade I) total resection of malignant meningiomas [180]. Lastly, Al-Mefty and colleagues investigating the malignant progression in meningioma from a benign to a higher histological grade, and concluded that the presence of complex genetic alterations (e.g., increased MIB-1 staining and chromosomal aberrations such as alterations in chromosome 22 and deletion of chromosomes (1p, 14q, and 10q), even with a benign histological grade, may potentially have an aggressive phenotype and require closer follow up [181].

Pituitary Tumors

The majority of pituitary tumors are adenomas arising from the anterior pituitary gland (adenohypophysis). In rare cases, pituitary carcinomas have been described [182]. Pituitary tumors arising from the posterior pituitary gland (neurohypophyseal) are also rare [183]. Pituitary adenomas are the fourth most common intracranial tumor after gliomas, meningiomas and schwannomas [184]. Pituitary adenomas are typically benign with even malignant pituitary tumors rarely metastasizing [184]. These tumors may secrete abnormally high amounts of hormones that may lead to physiological dysfunction resulting in patient morbidity. In addition to endocrinologic disturbances, mass effect leading to bitemporal hemianopsia is often observed in patients with pituitary neoplasms. Several risk factors have been identified including Multiple endocrine neoplasia type 1 (MEN1), Carney's complex, and Familial isolated pituitary adenoma [185].

Classification and Histology

A functional classification scheme has been developed based upon the secreted hormones and include lactotrophic adenomas (prolactinomas) which secrete prolactin, are the most common, and causes amenorrhea-galactorrhea syndrome in women and impotence in men, somatotrophic adenomas which secrete growth hormone, corticotrophic adenomas which secrete adrenocorticotropic hormone, gonadotropic adenomas which secrete luteinizing hormone and follicle-stimulating hormone, thyrotropin-secreting adenomas which secrete thyroid-stimulating hormone, cause thyrotoxicosis, and are rare, and null cell adenomas which do not secrete hormones. Excessive amounts of adrenocorticotropic hormone from pituitary corticotrophic adenomas can lead to Cushing's syndrome. As a consequence of undergoing adrenalectomy for treatment of Cushing's syndrome, 8-43% of patients will develop hyperpigmentation referred to as Nelson's syndrome [186,187]. An increased concentration of growth hormone from somatotrophic adenomas can lead to acromegaly. Interestingly, more than 95% of cases of acromegaly are due to a pituitary somatotroph adenoma [188].

Treatment

MR imaging with contrast on a pituitary protocol is the gold standard for evaluating pituitary tumors. Since the normal pituitary gland also enhances, the timing of the contrast is important in achieving a high-spatial-resolution image that is able to discern normal pituitary tissue from a macroadenoma [189]. In patients with non-secreting tumors and without neurologically deficits, it is reasonable to follow these patients with serial MRIs and visual field examinations.

Current treatment options for symptomatic pituitary adenomas include surgical resection, radiation therapy and medication therapy (first line for treating prolactinomas). Three dopamine agonists are routinely given to treat prolactinomas and include bromocriptine, carbergoline, and pergolide. Surgery using a transsphenoidal approach is typically the first line treatment for the other subtypes of pituitary adenomas [190,191]. Medical therapy is also used for patients with somatotrophic adenomas and includes dopamine agonists (e.g., bromocriptine), somatostatin analogues (e.g., octreotide), and growth hormone antagonists (e.g., pegvisomant). Medical treatment for thyrotropin-secreting tumors typically involves somatostatin analogues (e.g., octreotide).

For the treatment of pituitary adenomas, conventional radiation therapy typically consists of 40-50 Gy administered in 20-25 fractions over 4-6 weeks [192]. Although effective, complications associated with radiation therapy are high. One of the major post-radiation complications is hypopituitarism, which is both dose- and time-dependent. In addition, injury to the optic nerves and chiasm, lethargy, memory disturbances, cranial nerve palsies, and tumor necrosis with hemorrhage and apoplexy may also occur. The effects of radiation therapy on somatotrophic adenomas is cumulative with time and may
take 10 years to reduce the growth hormone levels into a "curative" range [193,194]. In contrast, for Cushing’s disease, radiation therapy restores ACTH levels to normal range between 18 and 42 months [195].

The use of radiosurgery for the treatment of pituitary tumors is still limited to tertiary centers and protocols are not standardized. Yang et al. conducted a large aggregated analysis of stereotactic radiosurgery treatment in patients with acromegaly and determined that the overall disease control rate was approximately 48%–53% for patients no longer taking suppressive medications after radiosurgery for acromegaly [196]. The post-radiosurgery remission rates for Cushing’s disease reported in the literature vary considerably from 0% to 100%, with most series documenting an approximately 50%–60% remission rate [197]. Long-term complications are thought to be similar to conventional radiation therapy (except for optic symptoms).

**Prognosis**

In cases where the tumor is compressing the optic apparatus, removal of the tumor improves vision in 90% of patients [198]. Furthermore, in one case series, only 27% of patients with prolactin-secreting tumors and 20% of patients with growth hormone-secreting macroadenomas returned to baseline hormone levels after surgical resection [198]. In the same series, the recurrent rate was roughly 13%. However, the inclusion of post-operative radiation therapy as well as degree of surgical resection of the tumor influenced the rate of recurrence. For example, for patients with partial surgical resection who did not receive post-operative radiation therapy, their recurrence rate was 50% [198]. On the other hand, there were no recurrences observed in patients with a gross total tumor removal who received postoperative radiation therapy [198].

The posterior pituitary can sometimes be damaged during surgery leading to a condition called central diabetes insipidus, which is characterized by excessive thirst and dilute urine.

**Primary Central Nervous System Lymphoma**

Primary Central Nervous System Lymphomas (CNS lymphomas) is a rare aggressive form of extranodal high-grade non-Hodgkin lymphoma that represents roughly 4% of intracranial neoplasms [199]. Several risk factors have been identified for primary CNS lymphomas including collagen vascular diseases (e.g., systemic lupus erythematosus and Sjögren’s syndrome), immunosuppression, including AIDS, and Epstein-Barr virus, which is associated with many lymphoproliferative disorders with nearly 100% association with primary CNS lymphomas [200], especially AIDS related [201]. On CT imaging, non-AIDS CNS lymphomas typically have a homogeneous enhancement pattern, whereas AIDS CNS lymphomas tend to have a necrotic center with the appearance of multifocal ring-enhancing lesions [202]. Surgery has a limited role in treatment and is used mainly for tumor biopsy. Radiation therapy and chemotherapy are primarily used to treat CNS lymphomas. Recent advances in treatment options have resulted in the use of high-dose chemotherapy in combination with autologous stem cell transplantation as an alternative treatment approach [199]. Whole-brain radiation therapy is often used with 40-50Gy, especially when chemotherapy is contraindicated [203]. For patients with non-AIDS CNS lymphomas the combination of radiation therapy and chemotherapy has a better overall survival than radiation therapy alone [204]. The median survival for patients not receiving treatment is 1.8-3.3 months, with radiation therapy alone median survival increases to 10 months, and with intraventricular methotrexate, the median time to recurrence increases to 41 months [205]. On the other hand, patients with AIDS-related CNS lymphomas have a much worse prognosis with a median survival of 2-5 months even after treatment [206,207].

**Vestibular Schwannoma**

Vestibular schwannomas, also known as acoustic neuromas, arise from cells that produce the myelin sheath covering the vestibulocochlear nerve (CN VIII). They usually originate in the superior vestibular division of CNVIII. These tumors are generally benign with an incidence rate of 1.67 per 100,000 person-years [1]. Vestibular schwannomas have been linked to loss of NF2 (tumor suppressor) on chromosome 22 [208,209]. Roughly 95% of vestibular schwannomas are unilateral, however, bilateral vestibular schwannomas is pathognomonic of neurofibromatosis type 2 (NF2) [201,202]. Most patients present with a classic clinical triad of hearing loss, tinnitus (high pitched), and disequilibrium [212]. Histologically these tumors contain Antoni A and B fibers [213]. Antoni A fibers are narrow elongated bipolar cells that are tightly packed, while Antoni B fibers are loosely packed cells with reticular fibers [213]. Verocay bodies (cellular areas surrounded by parallel arrangement of spindle shaped Schwann cells) are also seen histologically [214]. Since these tumors involve CN VIII, audiometric evaluation is part of the initial workup of this tumor and is used to help guide management. There are three approaches to treating vestibular schwannomas. These include complete surgical resection, radiation therapy, or monitoring using consecutive MRIs. With complete surgical removal, the incidence of recurrence is minimal from 0%-3% [215]. There are currently three surgical approaches used including retrosigmoid, which may preserve hearing, translabyrinthine, which sacrifices hearing but increases chances of preserving VII, and middle fossa approach, which is usually reserved for small lateral vestibular schwannomas [216]. The tumor progression rate following subtotal resection is roughly 20% [215].

**Neurofibromatosis**

Although there are six subtypes of neurofibromatosis, the most common are type 1 (NF1) and type 2 (NF2) and are discussed below.

**Neurofibromatosis type 1**

NF1 is an autosomal dominant disease that is linked with mutations in the NF1 gene on chromosome 17 which codes for neurofibromin [217]. Loss of neurofibromin, which is a negative regulator of the Ras oncogene, leads to increased growth stimulating signaling. Neurofibromatosis 1 represents more than 90% of neurofibromatosis [218]. The diagnosis of NF1 is made by two or more of the following [219]:

- 6 café au lait spots
- 2 neurofibromas of any type or one plexiform neurofibroma
- hyperpigmentation in the axillary or inguinal areas
- optic glioma
- >2 Lisch nodules (pigmented iris hamartomas)
 Neurofibromatosis type 2

NF2 is an autosomal dominant disease linked with mutations in the NF2 gene on chromosome 22, which codes for merlin (schwannomin) [211]. This tumor suppressor is typically produced in the central nervous system particularly in Schwann cells. The diagnosis of NF2 is made with either [220,221]:

- Bilateral vestibular schwannomas on imaging (MRI or CT)
- A first degree relative with NF2 and either:
  - Unilateral vestibular schwannoma at age <30 years or
  - Any two of the following: meningioma, glioma, posterior subcapsular lens opacity, neurofibroma

Additional criteria that carry less weight include:

- Unilateral vestibular schwannoma at age <30 and any of the following: meningioma, schwannoma, glioma, posterior subcapsular lens opacity or
- Multiple meningiomas and either of the following: unilateral vestibular schwannoma or any two of the following: glioma, neurofibroma, schwannoma, or cataract

 Neurofibroma

Neurofibromas are benign nerve sheath neoplasms arising in the peripheral nervous system. They are typically found in patients with neurofibromatosis. These tumors are divided into dermal (WHO grade 1) and plexiform (WHO grade 1). Dermal neurofibromas are usually associated with a single peripheral nerve and do not acquire malignant features. However, plexiform neurofibromas are associated with multiple nerve bundles and although low, have the ability to transform into malignant tumors, making these tumors more difficult to treat. The clinical course usually dictates the treatment approach for neurofibromas. Since these tumors are intimately intertwined with functional nerve, surgery is only performed if there are symptoms from the neurofibroma leading to progressive morbidity [222]. Other treatment options may include antihistamines, maturation agents (e.g., retinoic acid), and antiangiogenic drugs [222]. Targeted therapeutic approaches for specific molecular pathways vital to the tumor are promising, but need to be evaluated in clinical trials [222].

Schwannoma vs. neurofibroma

Both of these tumors are very similar and hard to distinguish without histological analysis. Schwannomas are typically well circumscribed and consist of Antoni A and B fibers. On the other hand, neurofibromas are typically less cellular, not as well circumscribed, and consist of wavy collagen fibers with occasional neuritis [223]. S-100 staining is oftentimes used to help distinguish these tumors since schwannomas typically display a greater percentage of positive cells and the intensity of staining is higher. However, with both tumors expressing some degree of S-100, this stain alone is not sufficient differentiating these tumors. Other stains that have been studied with varying sensitivities and specificities to help decipher these two tumors include calretinin, CD34, CD56, glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA), factor XIIIa, Leu-7, myelin basic protein and Glut-1 [223,224]. A combination of immunohistochemical stains provides the greatest support in determining schwannoma versus neurofibroma.

Secondary Brain Tumors

Epidemiology

Secondary, or metastatic brain tumors (MBTs), are the most common malignancies of the central nervous system (CNS). Typically, MBTs arise from primary tumor cells that migrate hematogenously or via direct invasion of adjacent tissue. According to population studies, the estimated prevalence of MBTs in the United States is 7-14 cases per 100,000 people [225,226]. Given the considerable advancement of diagnostic imaging, preventive screening, and increasing life spans in developed countries, these national statistics likely underestimate the actual incidence [227].

In patients with previously diagnosed cancer, 10-30% will also develop a brain metastasis [228]. This is partly due to the inherent capacity of malignant tumor cells to invade and cross basement membranes and migrate to healthy tissue. While patients typically present with non-specific symptoms, the most frequently observed findings include weakness, impaired balance, headaches, and seizures. Therefore, any patient with a history of a primary malignancy, who presents with neurological symptoms, should be thoroughly evaluated for a CNS metastasis.

Data collected by CBTRUS have determined that MBTs most often originate from malignancies of the lung (39% to 56%), breast (13% to 30%), skin, colorectal, kidney (2% to 6%), or unknown primaries (2% to 14%) [229,230]. Melanoma and primary colon cancers contribute approximately 6%-11% and 3%-8%, respectively (Table 3). Of note, the malignancy potential among primary etiologies varies with respect to the propensity to metastasize to the CNS. For instance malignant melanoma, which represents only 6% of all cancers [229], has the highest propensity of all systemic malignant tumors to metastasize to the brain [231]. This is supported by incidence rates of brain metastases secondary to malignant melanoma, which vary widely from 6% to 43% in clinical series [232-234] to 12% to 90% in autopsy series [231]. Lung cancer ranks second in overall metastatic lesions with roughly 10% of lung cancer patients presenting with CNS metastases. The incidence of MBTs rises to 20% during treatment and finally, MBTs are observed in an estimated 50% of patients at autopsy [235-237].

Table 3: Primary source of brain metastasis

<table>
<thead>
<tr>
<th>Primary Tumor Source</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Lung</td>
<td>39%-56%</td>
</tr>
<tr>
<td>Breast</td>
<td>13%-30%</td>
</tr>
<tr>
<td>Kidney</td>
<td>2%-6%</td>
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<tr>
<td>Melanoma</td>
<td>6%-11%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>3%-8%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1.20%</td>
</tr>
<tr>
<td>Unknown</td>
<td>2%-14%</td>
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It is important to note that the spectrum of metastasizing primary cancers and the risk of CNS involvement varies by patient age.
[238-240]. For instance, CNS metastases occur more frequently in adults, with the highest incidence seen in the fifth to seventh decades of life [238,239]. As mentioned previously, the most common primary sources of brain metastases in adults are cancers arising from the lung, breast, kidney, gastrointestinal tract, or skin, but may originate from any part of the body [229,230]. In children, the most common source of a brain metastasis is leukemia, followed by lymphomas and bone/soft tissue malignancies, including osteogenic sarcoma and rhabdomyosarcoma especially among children younger than 15 years [238]. Finally, germ cell tumors are the most frequent source of brain metastases in patients 15 to 21 years old [238].

The incidence of the primary cancers between males and females leads to differences in the sources of CNS metastasis. For example, breast cancer is the most common source of CNS metastases in women, whereas lung cancer is the most common source in men [239]. Comparing males and females diagnosed with melanoma, males are more likely to experience tumor spread to the CNS, as their primary tumors develop in locations that make it easier to spread to the brain, such as the head, neck, or trunk [231,241].

Imaging

MRI has high sensitivity to detect secondary CNS tumors. Namely, T1- and T2- weighted imaging modalities with and without contrast are used as the gold standard for initial evaluation. Generally, MBTs are detectable by gadolinium contrast enhancement and appear as round, well-circumscribed lesions surrounded by disproportionate areas of vasogenic edema. However, MBTs may have minimal or absent edema [242]. Accordingly, MBT should be included in the differential diagnosis for ring-enhancing lesions, as 30% of ring-enhancing lesions are diagnosed as secondary tumors [240].

Computed Tomography (CT) is a vital tool for initial work-up and perioperative management. On non-contrast enhanced CT (NECT), confined lesions may appear hypodense, isodense, or hyperdense relative to surrounding brain parenchyma [242]. Hyperdensity without contrast, especially at the gray-white junction and watershed zones of major vascular arteries, may suggest acute hemorrhagic lesions or CNS melanoma [243,244]. As with MRI, though, contrast enhanced CT is preferred to NECT for diagnostic purposes and is a viable alternative in cases where MRI is contraindicated.

Advanced MRI techniques such as Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Perfusion (MRP), Diffusion Weighted Imaging (DWI) and Diffusion Tensor Imaging (DTI) are employed for their specificity and to monitor treatment response. DTI, which hinges upon diffusion of water molecules along axons, is helpful to evaluate the integrity of White Matter (WM), as well as the location and orientation of WM tracts [245]. As an adjunct to other imaging, this technique has supplemented pre-surgical planning and characterization of intra-axial lesions to discern metastases from GBM [246]. MRP and DWI have utility in differentiating metastatic tumors from cerebral abscesses. In MRP studies, relative Cerebral Blood Volume (rCBV) is decreased for cerebral abscess and vice versa for metastatic lesions [247]. On DWI, restricted diffusion will be evident in the central non-enhancing portions of a cerebral abscess [248].

Treatment

Current approaches to the management of brain metastases are driven by prognostic factors, including the Karnofsky Performance Status (KPS), tumor histology, number of metastases, patient age, and status of systemic disease [249]. These approaches include surgery, Whole Brain Radiotherapy (WBRT), Stereotactic Radiosurgery (SRS), and chemotherapy. The standard of care for treating these lesions is usually surgery and/or radiosurgery. In cases of multiple lesions, WBRT may be a viable option. Unfortunately for the vast majority of metastatic brain tumors, there are no good chemotherapeutic options.

Surgical Resection: Informed clinical judgment is imperative when considering surgical resection of MBTs. Appropriate surgical candidates should be free of systemic cancer progression, have controlled primary disease, and independent function as evident by a KPS >70. Moreover, patients with solitary brain lesions generally benefit more from surgical intervention than those with multiple brain lesions [250]. Negative predictors include extensive extracranial disease and low Karnofsky performance scores (KPS<70).

As our evidence and knowledge of metastatic disease expands, surgery is now being considered as one of the primary treatments for brain metastases. As such, best practices for surgical resection are being evaluated. In two retrospective comparative studies from the MD Anderson, en bloc resection was compared to piecemeal resection in patients with supratentorial and infratentorial single metastases. These studies demonstrated that there was a significant increase in the risk of leptomeningeal dissemination in patients who underwent piecemeal tumor resection compared with en bloc resection [251] and a higher risk of local tumor recurrence with piecemeal resection than with en bloc resection [252].

When combined with post-operative WBRT, surgery has been shown to dramatically improve survival, local control, and duration of independent function in selected patients with solitary tumors [253,254]. Comparing treatment strategies in patients with 1-3 MBTs, combined surgery + WBRT (2 year recurrence rate 23%-42%) has outperformed WBRT alone (recurrence rate at <1yr, 43%) [255,256].

Radiation: Radiation therapy is commonly used to treat cerebral metastases. The addition of WBRT increases patient survival to 4 to 7 months. Some studies have shown that focal radiation treatment in addition to WBRT can increase survival for up to 12 months [250]. A Radiation Therapy Oncology Group trial (RTOG 9508) concluded several important aspects of radiation therapy in the treatment of cerebral metastases [250,255]. For instance, in the case of a single brain metastasis, SRS in addition to WBRT was shown to increase survival [250]. In the case of multiple brain metastases (limited in this case to 1-3), The RTOG 95-08 trial concluded that SRS in addition to WBRT provides palliative benefits and should be used for patients who have a KPS >70 [250,255]. For patients with more than 3 brain metastases, SRS has not been shown effective [250].

Chemotherapy: Several chemotherapeutic agents have been studied in combination with WBRT for patients with brain metastases. Long-term benefits from treating MBTs using chemotherapy are yet to be seen [249], though, as positive clinical responses from anti-cancer agents are quickly undermined by drug toxicity. This negatively impacts quality of life and results in minimal benefit to overall survival [249]. Incidentally, no chemotherapeutic agents have been approved for treatment of MBTs.

A major challenge to chemotherapeutic success is drug-delivery across the blood-brain barrier (BBB). Novel chemotherapeutic agents capable of crossing the BBB may promote survival and ultimately improve the bleak outlook posed by MBTs. Preliminary data from an inhibitor of topoisomerase I, topotecan, which crosses the BBB, has shown to be effective in treating brain metastases from small cell lung
and breast cancer [257]. An alkylating agent approved for treatment of malignant gliomas, temozolomide (TMZ), also has the capability to cross the BBB and may be effective against brain metastases secondary to melanoma [258]. Additionally, TMZ may be combined with cisplatin to treat metastases from non-small cell lung cancer, breast cancer, and melanomas [259]. Finally, a novel lipid-conjugated compound, DM-CHOC-PEN, has shown promising results in Phase I clinical trials [260–262]. After crossing the BBB, DM-CHOC-PEN is preferentially taken up by tumor cells, resulting in cytotoxicity via pseudo-alkylation of N7-guanine, while sparing normal brain parenchyma.

**Prognosis**

Until recently, the mainstay of MBT treatment had been whole-brain radiation therapy (WBRT) for symptom relief. When considering all patients with CNS metastases, WBRT alone improved median survival after diagnosis from 1 month to 3–6 months [228]. Given the poor prognosis and the peak incidence in elderly populations, most plans center on palliative options. To address this, the RTOG, a collaborative group founded by the National Cancer Institute established to improve clinical outcomes and quality of life in cancer patients, established the Recursive Partitioning Analysis (RPA) classification to guide selection of patients who would benefit from intervention. The reliable predictors to determine short-term vs long-term survival include extracranial disease activity, number of CNS foci (e.g., solitary vs. multiple), and performance status (i.e., KPS).

Without treatment, metastatic brain disease confers median survival of about one month. Whole-Brain Radiation Therapy (WBRT), however, only improves survival to 3–6 months, with most individuals succumbing to systemic illness rather than to CNS metastasis. The RPA classification has been validated in patients with breast, lung (NSCLC and SCLC), malignant melanoma, and unknown primaries. Additionally, it has been applied to cases where surgical resection and SRS have been main local treatment modalities. Table 4 represents the 3 classes defined by RPA.

<table>
<thead>
<tr>
<th>RPA Class</th>
<th>Description</th>
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| I         | Controlled primary tumor  
Age < 65 years;  
Karnofsky Performance Status (KPS) > 70  
Absence of non-CNS metastases |
| II        | Patients that do not fit classes I or II |
| III       | KPS < 70 |

**Table 4: Recursive partitioning analysis classification scheme.**

Patients who received WBRT after surgery, which in general had favorable prognosis (RPA Class I) prior to any treatment, represent the most homogeneous cohorts studied. Differences in survival outcomes among clinical trials, however, have been large. Overall median survival in RPA Class I ranged from 15–29 months; Class II was 5.5–11 months; Class III was 1.4–9 months [263–267].

Stereotactic Radiosurgery (SRS) may be another option for treatment of solitary or multiple tumors less than 3 cm or as an adjunct to other therapies, respectively. Retrospective reports evaluating the benefits of SRS in treating solitary metastasis have demonstrated a high rate of local control at one year (80%-95%) and a reduced risk for developing late side effects and severe neurologic complications (<10%) when administered without WBRT [268,269]. In a multicenter, retrospective analysis of radiosurgical outcomes from patients treated with WBRT followed by adjunct radiosurgery, Auchter et al. observed a 86% local control rate, with an actuarial median survival of 56 weeks and duration of functional independence (i.e., KPS >70) of 44 weeks [270].

Though strides have been made to improve survival and prolong independent function in patients with CNS metastases, the best treatment modality or regimen for a large, heterogeneous group of MBT patients is unknown [271]. Moreover, few options are available to patients with significantly impaired KPS. Indeed some retrospective studies have shown prolonged survival in patients with KPS <70 using SRS as an adjunct to WBRT (median survival 8.7 mo) compared to WBRT-alone [272], but no prospective trials involving this patient population have been performed. In most cases, the conservative approach is taken, which involves prescription of corticosteroids, namely dexamethasone, to mitigate the neurological symptoms secondary to intracranial mass effect. In patients treated with corticosteroids-alone, survival rates may be extended up to two to three months [273,274].

**Conclusions**

Brain metastases are a devastating complication of advanced systemic cancer and remain the most common intracranial tumor type. Patients develop metastatic disease in the setting of advanced pathology and thus palliative care is often the primary therapy offered. However, there has been a change in recent years in diagnostics and treatment strategies for systemic cancer with associated CNS involvement, in which, more effective treatments are allowing patients to experience limited or stable systemic disease. Currently, surgery and SRS offer the best outcomes, but their combined impact on survival leaves much to be desired. WBRT is still an important treatment modality for patients with multiple brain metastases as well as patients who cannot tolerate surgery and SRS largely due to the palliative nature of their disease. Continued research and development of novel chemotherapeutic agents may offer therapeutic advantages in the future, but to date none have led to significant gains for improving clinical outcomes.

**References**


87. Phillips HS, Kharbanda S, Chen R, Forrest WF, Soriano RH, Wu TD, et al: Molecular subclasses of high-grade glioma predict prognosis, delineate a...


