NEUROLOGY RESIDENT CURRICULUM IN NEURO-ONCOLOGY

Neuro-oncology is a growing subspecialty of neurology with a wide range of diseases, many of which are rare, that are associated with a broad spectrum of neurologic symptoms and complications. Many patients with brain tumors first present to general neurology with complaints of common neurologic symptoms, such as headaches or confusion, and others present to the emergency room with symptoms such as seizures or falls and are first evaluated by inpatient or consulting neurology teams. It is important for neurology residents to understand neuro-oncologic disease so that they feel comfortable in the initial approach to patients with brain and spine tumors, are able to recognize urgent or emergent situations, feel comfortable with common neurologic complications of cancer, and can share common language with neuro-oncology specialists when they need to make a referral. The purpose of this document is to share a curriculum of core competencies in neuro-oncology essential for all neurology residents to learn to practice general neurology and care for patients with neuro-oncologic disease.

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Part 1: General Approach

Clinical Evaluation

History

- Residents should be able to take an efficient and relevant history, including timing, onset, severity, and duration of symptoms
- Residents should gain comfort with agenda setting, introductions, responding to emotion, and discussing goals of care in the neuro-oncology clinic or inpatient/emergency consultation setting
- Residents should ascertain a patient/family's understanding of disease and prognosis, including previously imparted medical information
- Residents should obtain efficient and relevant family, spiritual/cultural, and social histories, and attend to potential psychosocial influences on care (e.g., insurance status, financial and caregiving resources, support structure, medical/health literacy, medical mistrust, gender-related competency, cultural humility, etc.)
- Residents should be able to localize symptoms and solicit focal neurologic symptoms when new brain tumor is on the differential
- For example, in adults with unprovoked seizures and/or new/worsening headache disorders
- Residents should recognize and solicit symptoms concerning for increased intracranial pressure or mass effect
- For example, headaches with red flags, cognitive/behavioral changes, changes in level of alertness, pressure waves, herniation syndromes
- Residents should obtain relevant collateral history from caregivers
- Residents' history should include personal oncological history, cancer screening, family history of cancer, or genetic syndromes

Physical Exam

- Residents should perform a comprehensive physical and neurological exam with attention to specific elements relevant in neuro-oncology:
- Vital signs and recognition of Cushing's triad
- Fundoscopic exam (papilledema, increased ICP)
- General medical exam including skin exam to assess for any evidence of systemic disease or a primary cancer
- Assess for pain in verbal and nonverbal patients
- Assess for any mood symptoms (depression, anxiety)

Clinical Scales

- Residents should be familiar with common scales used to assess functional status or performance status in neuro-oncology
- Karnofsky performance scale
- Residents should be able to elicit elements of the history of present illness and social history that highlight performance status, level of independence, and sources of physical and emotional/social support for patients and their families

Initial work up

Neuroimaging

- Residents should be able to order and interpret appropriate neuro-imaging for suspected CNS/PNS tumors
- Head CT without contrast: Commonly performed in the emergency setting to look for evidence of intracranial hemorrhage, acute hydrocephalus, or mass effects, which may require urgent neurosurgical attention. Generally not the imaging of choice for diagnosis of brain tumors.
- MRI brain with and without contrast: Imaging modality of choice for evaluation of brain tumors
- Residents should be able to recognize common, differentiating imaging features of meningiomas, glioblastoma, primary CNS lymphoma, and brain metastases, etc.
- Residents should be able to develop a differential diagnosis for tumor occurring in specifical anatomic locations in the nervous system and in adult and pediatric age groups (e.g., cortical tumors, ventricular tumors, cerebropontine angle tumors, pituitary tumors, pineal tumors, brainstem tumors, cerebellar tumors, spinal cord tumors, dural-based tumors, etc.)
- Residents should be able to discuss advanced imaging techniques that can be helpful in brain tumor diagnosis (use of MR perfusion, DWI, DTI, functional MRI)
- MRI is the modality of choice for suspected spinal cord or peripheral nerve tumors
- Laboratory and diagnostic investigations
- Residents should appropriately order body imaging (CT chest, abdomen, and pelvis or PET scan) (e.g., if there is suspicion for metastatic disease)
- Residents should be adept at deciding when to order routine EEG and/or long-term monitoring if there is clinic concern for seizures
- Residents should be comfortable ordering appropriate laboratory testing for evaluation for systemic cancer, pre-operative planning, and to rule out other disorders that may present similarly

Formulation

Neurologic emergencies

- Residents should be able to recognize signs and symptoms of neuro-oncologic emergencies and triage appropriate to emergency services, as well as initiate appropriate management
- Residents should be competent in recognition and management of the following emergency situations:

Malignant cord compression

- Recognize common signs and symptoms of cord compression: Acute back pain with focal neurologic deficits, acute myelopathy, cauda equina syndrome, progressive spinal cord symptoms in patient with cancer (generally acute or

subacute). Evaluate for and interpret signs of spinal cord dysfunction including upper motor neuron signs, sensory level, rectal tone, and lumbosacral reflexes if concern for cauda equina.
- Initiate appropriate emergent management measures, such as promptly initiating high-dose steroids while awaiting confirmatory imaging with MRI
- Initiate appropriate consults to neurosurgery/spine surgery and/or radiation oncology
- Increased intracranial pressure
- Recognize signs and symptoms of increased intracranial pressure, including Cushing's triad, red flags in the history, and physical signs like papilledema
- Initiate work up to evaluate for a mass, bleed, and/or hydrocephalus
- Manage initial critical presentation with prompt initiation of corticosteroids ,if appropriate, and/or urgent/emergent neurosurgical consultation

Seizures
- Residents should have high clinical suspicion to evaluate for seizures in patients with neurologic symptoms and brain tumors, and likewise should have high clinical suspicion to evaluate for tumor in patients with new onset seizures. Residents should recognize focal seizures, epilepsia partials continua, and status epilepticus. Residents should understander and implement timely use of anti-seizure medications and escalate medical therapy and level of care as needed for refractory seizures.

Primary malignant brain tumors
- Residents should recognize common imaging features of primary brain tumors on MRI, consider when biopsy or resection would be appropriate for initial diagnosis, and triage referrals to neurosurgery in a timely manner. Residents should be able to consider risks of resection based on neuroanatomic location of tumor and collaborate with neurosurgery colleagues for timely referrals and consultation.
- Recognize imaging features of adult primary brain tumors including, but not limited to: high grade glioma/glioblastoma, low grade glioma (oligodendroglioma, astrocytoma), primary CNS lymphoma, ependymoma, and pediatric primary brain tumors: medulloblastoma, pilocytic astrocytoma, diffuse midline glioma, ependymoma
- If a tumor that is known to disseminate in the neuroaxis is suspected (medulloblastoma, ependymoma), residents should recognize need for spine imaging and CSF sampling

Metastatic brain tumors
- Residents should consider diagnosis of brain metastases in patient with brain tumors and history of cancer, patients with systemic signs/symptoms of disease (weight loss, shortness of breath, hemoptysis, skin lesion, etc.), multiple brain tumors, and solitary tumors of unknown etiology
- Initiate systemic imaging with CT chest, abdomen, pelvis and/or PET scan if metastatic disease is on the differential
- Involve neurosurgery as well as medical/surgical oncology for decisions about where to best obtain tissue for diagnosis
- Residents should recognize symptoms that are concerning for leptomeningeal metastases (increased ICP, cranial neuropathies, cauda equina syndrome, etc.) and consider need for CSF sampling and imaging of brain and spine

Primary benign brain tumors
- Residents should recognize common imaging features of benign brain tumors (meningioma, pituitary adenoma), and have a general understanding of when neurosurgery is urgent (i.e., large, symptomatic tumors) vs when observation may be appropriate (i.e., incidentally discovered small meningioma)

Cancer Neuroscience
- When approaching a patient with a brain tumor and formulating an initial diagnostic and management plan, residents should understand the factors that make brain tumors unique from other systemic cancers, and the prognostic and treatment challenges this poses.
- Residents should be familiar with the basic components of the brain tumor microenvironment
- Residents should be familiar with immune signaling and immune environment in brain tumors

- Residents should understand the role of the blood brain barrier and relative permeability of the blood brain barrier in some cancers.
- Residents should be able to discuss paracrine signaling and the role of neurotransmitters and growth factors
- Residents should discuss the changes that cancer can have on the nervous system. For example, these changes may contribute to neurologic complications of cancer, such as paraneoplastic syndromes, cancer-related fatigue, seizures, and neurocognitive changes in patients with cancer.

Initial approach to management

Symptom management

- Residents should recognize common symptoms related to brain tumors and be able to initiate management in the clinic or hospital setting
- Management of cerebral edema and increased intracranial pressure—appropriate use of steroids and steroid dosing, as well as management of steroid-related complications in the inpatient and outpatient settings (hyperglycemia, pneumocystis prophylaxis (PJP), gastrointestinal ulcers, adrenal insufficiency, insomnia, weight gain, fluid retention, etc.)
- Management of tumor-related epilepsy—consider drugs that can reach therapeutic doses quickly, drugs that commonly interact with chemotherapeutics, and lack of evidence for prophylactic anti-seizure medications
- Management of headache—consider etiology of headache, including elevated ICP, cerebral venous sinus thrombosis from hypercoagulability, exacerbation of migraine as a complication of treatment, side effects of therapy, etc., and manage both the headache symptom and the underlying cause of a secondary headache disorder

Multi-disciplinary care

- Residents should be comfortable involving and consulting appropriate multidisciplinary services for care of patients with brain tumors in a timely fashion (i.e., neurosurgery, radiation oncology, medical and neuro-oncology, palliative care, physical therapy, occupational therapy, speech therapy, social work/case management, etc., and use of multidisciplinary tumor board discussions)

Diagnostic evaluation

Neuro-pathology

- Residents should be familiar with the World Health Organization Classification of CNS tumor
- Grading system
- Integrated molecular and histologic diagnosis
- Adult type and pediatric type primary brain tumors

Histology

- Residents should recognize key histologic features of each grade of glioma (i.e., grade 2: infiltrative; grade 3: increased nuclear atypia, hypercellularity, mitotic activity; grade 4: microvascular proliferation, pseudopalisading necrosis)
- Residents should recognize the hallmark histologic features of certain tumors of primary neurologic origin (i.e., pilocytic astrocytoma: Rosenthal fibers; glioblastoma: pseudopalisading necrosis; oligodendroglioma: "fried egg" nuclear clearing, calcifications; etc.)

Molecular markers

- Residents should be familiar with key molecular markers that are of prognostic or predictive significance or that are defining mutations of a tumor type. The following are examples of important markers and associations to know:
- IDH mutation—oligodendrogliomas and astrocytoma
- IDH wild type—Glioblastoma
- 1p19q co-deletion—oligodendroglioma
- MGMT methylation status—predictive marker in glioblastoma
- H3K27M mutations—diffuse midline glioma
- Role of BRAFv600 mutations and BRAF fusions (KIAA1549-BRAF) in pediatric gliomas

Genetic syndromes

- Residents should understand germline vs mosaic vs somatic mutations and how these affect cancer risk
- Residents should recognize tumors and mutations that are commonly associated with familiar cancer syndromes and be able to initiate appropriate clinical screening and referrals to genetics. The following syndromes are relevant for general neurologists to know. For each, residents should understand the clinical manifestations of the syndrome including whether they predispose to childhood tumors, related gene(s)/protein(s)/molecular pathway(s), mode of inheritance (i.e., autosomal dominant vs recessive), associated tumors, diagnostic criteria, screening recommendations, and available targeted therapies based on the pathway that is altered.
- Neurofibromatosis type 1
- Neurofibromatosis type 2 related schwannomatosis (NF2)
- Schwannomatosis
- Von Hippel Lindau
- Tuberous sclerosis
- Li Fraumeni
- Lynch syndrome
- DICER
- Gorlin

Treatment planning and prognosis

Approaches to prognostication in neuro-oncology

- Residents should have basic competency in how to conduct a serious illness conversation. There are many different approaches to communication/conversations about serious illness and prognosis which are outside the scope of this curriculum, but should be included in neurology residency didactics. We recommend skill-based didactics focused on communication techniques for difficult conversations that is delivered by an expert.
- Residents should demonstrate an awareness of resources for navigating challenging serious illness communication scenarios (see appendix for resources)
- Residents should demonstrate an awareness of techniques to communicate about prognosis, including strategies to address prognostic uncertainty (e.g., best case/worst case, offering time-limited trials)
- Residents should demonstrate ability to recognize and appropriately respond to strong emotions and navigate family conflict
- Residents should facilitate medical decision-making to reflect a patient's values and goals of care, as well as an awareness when senior or expert guidance is required
- Residents should demonstrate awareness of the importance of cultural competency and the impact of cultural beliefs in communication and shared decision-making

Palliative care in neuro-oncology

- Residents should be able to define palliative care (so as to distinguish it from hospice care) and how this is integrates into caring for patients with neuro-oncologic disease
- Residents should understand the aspects of primary palliative care, including symptom management (fatigue, headache, nausea, sleep, cognition, etc.), prognostic awareness, goals of treatment, alleviation of suffering, and advanced care planning (code status, advanced directives, expectations and wishes at end of life)
- Residents should describe the differences between palliative care and hospice and the relationship of palliative care and hospice care across the disease course
- The principles of palliative care in neuro-oncology are broadly applicable to many other subspecialties within neurology and should be integrated accordingly
- The resident should be aware of the benefits and limitations of population-level prognostication and prognostication scores, algorithms, and biomarkers, and should be able to communicate these in an understandable way.
- Treatment modalities for brain tumors

Surgery

- Residents should know that tissue diagnosis is the gold standard for diagnosing tumors of the CNS and collaborate with neurosurgery for diagnostic evaluation
- Residents should have a general understanding of which patients will benefit most from surgical resection (based on suspected tumor type, location, patient-specific factors, and comorbidities related to surgical risk and preferences, multifocality vs solitary tumors, etc.) vs biopsy and initiate timely referrals to neurosurgery for discussion

Radiation therapy

- Residents should understand different delivery mechanisms of radiation (i.e., stereotactic radiation, focal radiation, whole brain radiation) and the associated risks and side effects
- Systemic therapy: chemotherapy, immunotherapy, targeted therapy, biological therapy
- Residents should be familiar with the first line chemotherapy for adult infiltrative gliomas (temozolomide) and have a general understanding of risks and side effects associated with his medication (cytopenia, nausea, vomiting, fertility and fetal risks)
- Residents should be familiar with basic mechanisms of action of immune check point inhibitors and VEGF monoclonal antibodies (eg, bevacizumab)
- Residents should understand tumor suppressor genes and oncogenes that are associated with cancer pathways that may be treatable with targeted therapies

Tumor treating fields

- Resident should have a basic familiarity with this treatment modality for glioblastoma
- Clinical trials and experimental therapeutics
- Residents should appreciate the role of clinical trials and clinical research in the management of patients with brain tumors, particularly as clinical trials are used in malignant brain tumors that do not have effective therapy or therapy with curative intent
- Residents should know the phases of clinical trial design (Phase 0-4) and the purpose of each phase
- Residents should understand informed consent processes and principals of informed consent

Management of neurological complications and side effects

- Residents should be familiar with neurological complications of cancer that they may encounter on an inpatient consultation service or may see in a neurology outpatient clinic. Specific complication risks of importance to residents:
- Stroke—due to hypercoagulable state, and sometimes further increased by specific treatments, such as certain chemotherapy or targeted therapy medications or radiation therapy
- Venous thromboembolism, including risk of cerebral vein thrombosis, pulmonary embolism, deep vein thrombosis

Neuropathies

- Brain tumor associated epilepsy
- Residents should be able to manage neurological side effects of cancer therapy and recognize associations with these treatments:
- Radiation: Residents should be familiar with neurological complications of radiation therapy including pseudoprogression, radiation necrosis, memory impairment, leukoencephalopathy, and SMART syndrome
- Chemotherapy-induced peripheral neuropathy (high risk with platinum-based chemotherapy, taxols, vinca alkaloids, thalidomide)
- Methotrexate toxicities, including acute and long-term neurocognitive syndromes.
- Cytarabine-associated cerebellar toxicity
- Ifosfamide encephalopathy
- Neurological toxicities of immune check-point inhibitors
- CAR-T cell associated neuro-toxicity (ICANS)

End-of-life care and hospice

- Residents should be proficient with inpatient management of end-of-life symptoms including delirium, pain, dyspnea
- Residents should be able to identify appropriate timing for and be able to initiate conversations about transitions to hospice care.

Pediatric Neuro-Oncology

Many of the approaches in adult neuro-oncology also apply to pediatric patients, but there are certain aspects of care that are unique to the pediatric population. Residents should recognize the specialized approach to neuro-oncologic disease in children including the following:

- A detailed developmental history including loss of or inability to reach milestones as well as family history of malignancy/genetic syndromes
- An age appropriate neurologic exam with specific attention to enlarging head circumference
- MRI as the preferred imaging modality given the desire to avoid cumulative radiation exposure from CT imaging
- Most pediatric tumors require spinal imaging which should be considered at time of diagnostic evaluation given the need for sedation for imaging in many children
- The specific tumor types that are more common in children
- Treatment approach in children prioritizes a radiation-sparing approach given long-term sequelae

Part 2: Neuro-Oncologic Tumors and Syndromes

Tumor Types

Glioma

- Residents should understand the epidemiology, clinical presentation, approach to diagnosis, classic imaging features, histopathologic criteria, standard approach to treatment and common side effects, and prognosis for the following:
- Oligodendroglioma, WHO grade 2 and 3
- Astrocytoma, WHO grade 2, 3 and 4
- Glioblastoma, WHO grade 4
- Diffuse midline glioma, WHO grade 4
- Pilocytic Astrocytoma, WHO grade 1

Primary CNS Lymphoma and Primary Ocular Lymphoma

- Residents should understand the epidemiology, clinical presentation, approach to diagnosis including systemic disease screening, classic imaging features, and basic treatment strategies (e.g., steroid avoidance prior to diagnosis, high dose methotrexate-based regimen)

Meningioma

- Residents should understand the epidemiology, clinical presentation, approach to diagnosis, WHO grading system (1, 2, and 3) and typical histopathological features, as well as basic management strategy (e.g., when surgery and/radiation is indicated vs a surveillance approach)
- Cranial and Paraspinal Nerve Tumors
- Resident should understand the clinical presentation, associated genetic syndromes, approach to diagnosis including classic imaging features, and basics of management including indications for surgery and alternative treatment options for the following:
- Acoustic neuroma/vestibular schwannoma
- Peripheral schwannoma
- Plexiform neurofibroma
- Malignant peripheral nerve sheath tumor (MPNST)

Spinal Cord

- Resident should formulate an appropriate differential diagnosis based on tumor location and neuroimaging characteristics, for example:
- Extradural: metastases, chordoma, sarcoma, lymphoma, myeloma, histiocytosis, etc.
- Extramedullary, intradural: nerve sheath tumors, meningioma, etc.
- Intramedullary: astrocytoma, ependymoma, hemangioblastoma, etc.

Ependymal Tumors

- Residents should understand the epidemiology, clinical presentation, classic imaging features including need for total spine imaging given dissemination risk, WHO classification based on location, and general approach to treatment (e.g., surgery +/- radiation)
- Ependymoma: supratentorial (ZFTA fusion, YAP1 fusion), posterior fossa type A and B, spinal
- Myxopapillary ependymoma
- Subependymoma

Embryonal Tumors

- Residents should understand the epidemiology, clinical presentation, classic imaging features including risk for dissemination in the neuroaxis, WHO classification including molecular features, and general approach to treatment (eg, surgery followed by radiation/chemotherapy)
- Medulloblastoma, WNT activated
- Medulloblastoma, Sonic Hedgehog (SHH)
- Medulloblastoma, non-WNT/non-SHH (group 3/C and 4/D)
- Atypical Teratoid Rhabdoid Tumor (ATRT)

For the rarer tumor types listed below, residents should be aware of their clinical presentation and typical imaging features, with the goal of being able to include these diagnoses in the differential when appropriate.

Glioneuronal and Neuronal Tumors

- Ganglioglioma
- DNET
- Germ cell tumors
- Germinoma
- Non-germinoma germ cell tumors (NGGCT)

Tumors of the Sellar Region

- Craniopharyngioma
- Pituitary adenoma

Pineal Parenchymal Tumors

- Pineoblastoma
- Pineocytoma
- Pineal parenchymal tumors of intermediate differentiation

Choroid Plexus Tumor

- Choroid plexus papilloma
- Atypical choroid plexus papilloma
- Choroid plexus carcinoma

Paraneoplastic Syndromes

- Residents should be familiar with the more common paraneoplastic syndromes and their associated cancers
- Clinical syndromes include limbic encephalitis, opsoclonus-myoclonus-ataxia, brainstem encephalitis, cerebellar syndromes including subacute cerebellar degeneration, Lambert-Eaton Myasthenic Syndrome (LEMS), etc.
- Residents should recognize that more than one antibody can be associated with a single syndrome and vice versa
- Resident should know the difference between high risk and intermediate risk antibodies and how this relates to treatment and prognosis
- Residents should appropriately evaluate for a paraneoplastic syndrome with imaging, serologic and CSF studies when the clinical suspicion for such syndrome is high
- Residents should be familiar with the general treatment approach to paraneoplastic disorders including treatment of the underlying malignancy and immunosuppressive medications
- Residents should recognize the need to develop a screening plan if a paraneoplastic syndrome is identified without the presence of an active malignancy

Brain Metastases and Leptomeningeal Disease

- Residents should be familiar with basic epidemiology of brain metastases including frequency of brain metastases in the solid tumor population and which solid tumors are most likely to metastasize to the CNS (i.e., breast, lung, melanoma, renal cell, etc.)
- Residents should understand the difference between solid tumor CNS metastases and liquid tumor CNS metastases (lymphoma, leukemia) in terms of clinical presentation, diagnosis, and general approach
- Residents should appropriately consider treatment options for brain metastases and understand the importance of a multidisciplinary care team:
- Surgery (for example when solitary metastases, symptomatic, and accessible)
- Radiation (e.g., stereotactic radiosurgery, whole brain)
- Systemic therapies (a general approach, including the need for CNS penetrating regimens)
- Residents should have a high clinical suspicion for leptomeningeal carcinomatosis in a patient with cancer and presenting symptoms of leptomeningeal disease involvement as mentioned above
- Residents should appropriately understand the urgency of work-up and indicated testing (MRI, CSF studies) for suspected leptomeningeal carcinomatosis
- Residents should formulate a general treatment plan for leptomeningeal disease including elevated ICP management, symptomatic management (pain control, etc.), and disease-directed therapy (radiation, chemotherapy, targeted treatments)
- Residents should understand the poor prognosis associated with leptomeningeal disease and involve supportive care services early in disease course