The Right Amount At the Right Time

Evidence Based Treatment in Neuro Oncology

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Course Objectives

By the completion of the 2 hour lecture, attendees will:

1. Understand the medical management of neuro-oncologic conditions and the implications on physical therapy.
2. Apply the principles of neuroplasticity to the rehabilitation of patients with neuro-oncologic diagnoses.
3. Prescribe a targeted exercise intervention for improving functional mobility in patients with neuro-oncologic diagnoses across the continuum of care.
4. Implement and modify physical therapy interventions based on the phase of a patient's medical course.

Medical Management

1. Understand the medical management of neuro-oncologic conditions and the implications on physical therapy.

Brain tumor: General Treatment[1,3]

- Surgery – for nearly all who will have restorative and supportive rehab
  - Placed on steroids to decrease cerebral edema
- Chemotherapy (CT): not generally used for benign or metastatic brain tumors
  - Only recently used for primary brain tumors
- Radiation: several weeks
  - Causes fatigue that can last for weeks to months
  - Also causes cognitive impairment and impaired memory
  - Acute side effects due to cerebral edema
    - Treated with steroids – steroid myopathy is common and often seen in outpatient PT
    - Can have radiation necrosis chronically that is difficult to distinguish from tumor recurrence

Spinal Tumor: General Treatment [2,3]

- Steroid Treatment
  - Typically part of initial treatment of spinal tumors to reduce tumor and spinal cord vasogenic edema
- Surgery
  - Primary goals to preserve neurologic function, reduce pain, and ensure mechanical stability
- Chemotherapy
  - Plays a limited role largely because of the urgent need to decompress the spinal cord
  - Chemotherapy is considered in the setting of highly chemosensitive tumors, such as lymphomas, neuroblastomas, and germ cell tumors
- Radiation
  - Extent of an epidural mass and neurologic involvement influence the response to radiation
  - Radiation impacts the area of the compression and 2 vertebra above and below the level of injury
  - Radiation myelopathy can cause delayed necrosis of the spine or peripheral nerves 5-48 months after surgery

Chemotherapy[3-6]

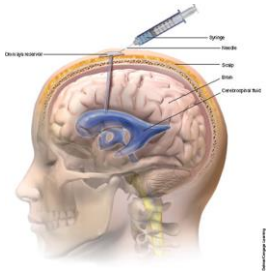
- Cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing
- Longer survival rates in last 20 years due to improved chemotherapy regimens
- Gliomas
  - Temozolomide (TMZ): alkylating agent, can permeate blood brain barrier
    - Used in combination with radiation for high grade gliomas
    - Significant fatigue occurs in 13% of patients
  - Carmustine polymer wafers (Gliadel wafers)
    - Used with high grade gliomas though questionable whether this adds survival benefit compared to standard of care
    - More often used as salvage therapy
  - Bevacizumab: monoclonal antibody
    - Used primarily as second line treatment, decreases corticosteroid requirement
  - Salvage chemotherapies: Platinums (cisplatin, carboplatin), etopside

Chemotherapy, Cont.

- Medulloblastoma[3,4]
  - Unclear role for adjuvant chemotherapy in adults
  - Typically cisplatin-based regimens
- Primary CNS lymphoma[3,4,6]
  - Systemic high-dose methotrexate (MTX)-based regimens
    - Penetrates CNS at sufficiently high doses
    - Often used in combination with other systemic chemo drugs: TMZ, cytarabine, vincristine, rituximab (Rituxan, monoclonal antibody)
  - Intrathecal chemotherapy typically only used when there is leptomeningeal involvement

Ommaya Reservoir

- Intraventricular system used for the delivery of chemotherapy directly to cerebral spinal fluid
- Consists of a small plastic dome inserted underneath the scalp and a catheter connecting to one of the ventricles
- Can also be used to obtain samples of cerebral spinal fluid
- Precautions: For 8-10 days after it is placed no bending forward >90 degrees and no valsalva.



Chemotherapy Complications

Cardiotoxicity[3,7-8]

- Blood pressure changes
  - HTN is one of the most common adverse effects of therapy
- ECG changes
  - QT prolongation
- Arrythmias
- Myocarditis/Pericarditis
- Myocardial infarction
- Congestive heart failure
- Cardiomyopathy

Cardiomyopathy 3, 9-12

- Anthracyclines[8,9]
  - Doxorubicin and danorubicin are the most common drugs in this class
  - Used for breast, ovarian, bladder, lung, thyroid, and gastric cancers, as well as soft tissue sarcomas, Hodgkin's lymphoma, and non-Hodgkin's lymphoma
  - Cardiomyopathy can develop during or years after treatment
    - Increased risk with advanced age, increased dosage, chest irradiation, underlying heart disease
- Treatment:[3,10]
  - Afterload and volume reduction
    - Beta blockers
  - Reduce oxidant stress of chemotherapy
    - Animal studies show some protective effects of aerobic exercise initiated prior to patients receiving chemotherapy with anthracyclines[11,12]

Pulmonary toxicity

- Bleomycin[3,13]
  - Used to treat melanoma, sarcoma, testicular and ovarian cancer, Hodgkin's and non-Hodgkin's lymphoma
  - Leads to interstitial pulmonary fibrosis in up to 10% of patients
  - Risk factors: advanced age, cumulative drug dose, impaired renal function, combined radiation therapy or other chemotherapeutic agents
- High Dose Methotrexate[14-15]
  - Most common presentation is hypersensitivity pneumonitis
    - Symptoms: dyspnea, nonproductive cough, fever, hypoxemia, fatigue
    - Typically occurs within first year of treatment, but can develop anywhere between 12 days and 18 years after administration
  - Can be treated and prevented with folic acid supplementation
- Treatment with corticosteroids and stopping or decreasing the dose of the offending chemotherapy agent[13,15]

Neurotoxicity

- High Dose Methotrexate[15]
  - Presents as aseptic meningitis, transverse myelopathy, acute and subacute encephalopathy and leukoencephalopathy, somnolence, confusion, seizures
  - Usually seen within first 24hrs of treatment and resolve spontaneously without sequelae
  - The major delayed complication is leukoencephalopathy (gradual impairment in cognitive function, accompanied by somnolence, seizures, ataxia, and hemiparesis
- Platinum Chemotherapies (cisplatin, carboplatin) [16,17]
  - Used to treat testicular, ovarian, bladder, esophageal, lung, and head and neck cancers as well as non-Hodgkin's lymphomas
  - Second line treatment for gliomas
  - Ototoxicity also a common side effect
    - High frequency sensorineural hearing loss with tinnitus
    - Incidence of 19%–77% of patients treated with cisplatin, and 19%–42% may develop permanent tinnitus
    - Lhermitte's sign

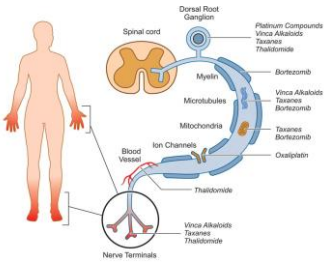
Neurotoxicity: Chemotherapy Induced Peripheral Neuropathy (CIPN)

- Vinca Alkaloids (vincristine) [16,18]
  - Used to treat a wide variety of cancers
  - Virtually all patients treated with vincristine develop some degree of sensory and/or motor CIPN
  - Autonomic neuropathies can also occur with vincristine
    - Abdominal pain and constipation can occur in 50% of patients
    - Orthostatic hypotension, dry mouth, urinary retention, sexual dysfunction can also occur
  - Rarely cranial nerves can develop mononeuropathies, most commonly the oculomotor nerve
- Taxanes (paclitaxel, docetaxel) [16,18]
  - Used to treat lung, ovarian, and breast cancer
  - 60% of patients treated with paclitaxel develop some form of sensory CIPN, 15% with docetaxel
  - Motor CIPN in up to 14% of patients treated with paclitaxel
- Platinums [18]
  - Neuropathy typically develops after cummulative dosing of 300 mg/m2, with nearly 100% incidence with doses 500-600 mg/m2
  - Sensory neuropathies

Neurotoxicity: CIPN Cont. [3,19,20]

- CIPN is treated by reducing dose or stopping treatment with offending agent
  - Often improves CIPN but may never completely resolve
- Neuropathy can still progress over weeks to months and may develop after therapy completes
- Also treated with gabapentin, pregabalin, SSRIs, and tricyclic antidepressants
- Physical therapy intervention
  - Patient education
  - Gait and balance training
  - AD prescription
  - Bracing

CIPN: Mechanisms of Action



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Chemotherapy Toxicities Continued

- Nephrotoxicity[3,21]
  - Most commonly caused by platinum drugs
  - Can lead to acute renal failure
  - Prevented and treated with intensive hydration
  - Delayed drug excretion can result in increased systemic toxicity
    - Particularly with high dose methotrexate
- Rheumatic Toxicity[3]
  - Common clinical condition post chemotherapy
    - Myalgias, arthralgias, joint stiffness, generalized musculoskeletal achiness and periarticular tenderness

Chemotherapy Related Cognitive Impairment

- Neuroimaging findings:[22-23]
  - Diffuse decrease in GM and WM volume
  - Early decrease in frontal activation
  - Altered white matter tract mircostructure
- Cognitive domains affected[23-25]
  - Memory
  - Attention
  - Processing speed
  - Visual-spatial abilities
  - Learning abilities
  - Motor function
  - Executive function
- Long term effects persist in 17-34% of patients[22]
- Subjective changes ≠ objective changes[22-25]

Radiation[3]

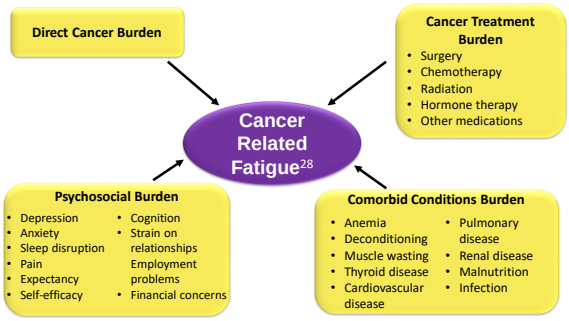
- Radiobiology
  - Higher dose per fraction = greater impact on tumor and healthy tissue.
  - Smaller doses are used when there are sensitive organs nearby or when a large volume of tissue needs radiation
  - Tissues that are sensitive to radiation have a high rate of turnover
    - A cell that has more time to repair damage is less sensitive to radiation effects
    - Goal is to target cells at different stages of differentiation
      - Cells are sensitive at different times of the cycle
      - Important to fractionate radiation treatment
  - Tissue volume: the more irradiated, the more likely to see side effects
    - Ex: whole organ radiation more likely to have organ failure than partial organ radiation

Radiation Side Effects[3,26,27]

- Acute effects: usually transient
- Chronic effects: usually in sensitive tissues like connective tissue (fibrosis) and neural tissues (neuropathy)
  - Fibrosis is often irreversible
  - Secondary cancers
- Radiation Therapy Encephalopathy (RTE):[3,26]
  - RTE may be reversible when it is a complication of recent radiotherapy or can result in permanent neurologic impairments
  - Acute radiation encephalopathy is often treated with steroids to reduce edema
  - Multiple studies reporting decline in cognitive function after whole brain radiation therapy (WBRT)[26,27]

Cancer Related Fatigue (CRF)

- "A distressing persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning." – National Cancer Comprehensive Network
- Prevalence 40-90% for general oncology population[28]
  - 39-94% with malignant gliomas[29,30]
  - >75% in those with advanced cancer[31]
- Can persist for months or years after treatment is completed[28]



Neoplastic related fatigue (R53.0): ICD-10 Criteria

- The following symptoms have been present every day or nearly every day for a two week period within the last month:
  - Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level; plus 5 or more of the following:
    - Complaints of generalized weakness, limb heaviness
    - Diminished concentration or attention
    - Decreased motivation or interest to engage in usual activities
    - Insomnia or hypersomnia
    - Experience of sleep as unrefreshing or non-restorative
    - Perceived need to struggle to overcome inactivity
    - Marked emotional reactivity (e.g. sadness, frustration, irritability) to feeling fatigued
    - Difficulty completing daily tasks attributed to feeling fatigued
    - Perceived problems with short-term memory
    - Post-exertional fatigue lasting several hours

Causes of CRF: Inflammatory Processes with Brain Tumors[29]

- Proinflammatory cytokines are activated by tumors and cancer treatments
  - Cytokine signaling in the CNS can lead to fatigue symptoms
- Inflammatory response in CNS can persist for years after cancer treatment is completed and correlates to persistent fatigue levels
- Treatment with neurostimulants (modafinil, methylphenidate) during brain radiation treatment has mixed results in improving fatigue

CRF Treatment[28]

- Collaborate with physicians and other multi-disciplinary providers to address potentially reversible causes of fatigue
  - Anemia, electrolyte abnormalities, cardiac and pulmonary issues, nutrition, pain, sleep disturbances, deconditioning
- Education
  - Energy conservation and pacing
  - Compounding effect of sedentary habits
  - "Exercise Snacks"
  - Daily exercise log or visual goals may increase adherence

Balance between Repetition/Intensity and Fatigue

- Aerobic and resistance training can improve fatigue in patients with breast and solid organ cancers[32-38]
- Reduced fatigue symptoms with exercise programs both during and after treatment with chemotherapy and/or radiation
  - Aerobic exercise may be slightly more beneficial than resistance training[39-40]
  - Better results with moderate to high intensity exercise compared to low intensity[32,41]
  - Improved fatigue and QOL for hospitalized patients[42,43] and patients with advanced cancer[44,45]

Balance between Repetition/Intensity and Fatigue

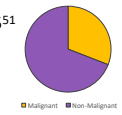
- High intensity interval training can be safe and effective in reducing cancer related fatigue[46-49]
- F: 2-3x/week, sessions as short as 16 minutes
  - I: high 60-85% 1RM/HRmax
  - T: resistance or aerobic
  - T: During chemotherapy/radiation and after treatment
- High compliance despite high intensity exercise, possibly due to lower time commitment
- Studies have been with supervised exercise programs due to increased intensity
- Benefits can persist up to one year after completion of program[50]

Karnofsky Score		ECOG Score	
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activity, minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
Normal activity with effort	80		
Unable to carry on normal activity or perform active work; cares for self	70	2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of walking hours
Requires occasional assistance but is able to care for most own needs	60		
Requires considerable assistance and frequent medical care	50	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Disabled; requires special medical care and assistance	40		
Severely disabled; hospitalization indicated although death not imminent	30	4	Completely disabled; cannot perform any self-care; totally confined to bed or chair
Very sick; hospitalized and active	20		
Moribund; fatal processes progressing rapidly	10		
Dead	0		

Primary CNS tumors and Metastases

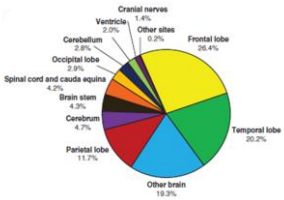
Evaluation and Tx of Primary Central Nervous System Tumors

- Clinical presentation:[1,3]
  - General:
    - Brain: personality changes, seizures, headaches
    - Spine: myotomal weakness, dermatomal sensory loss, pain
  - Localized: dependent on tumor location, localized weakness, sensory symptoms, ataxia, vision changes
- Precentage of Tumors diagnosed in 2011-15[51]
  - Malignant 30.9%
  - Non-Malignant 69.1%

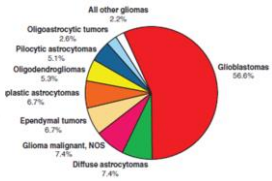


Brain tumors[51]

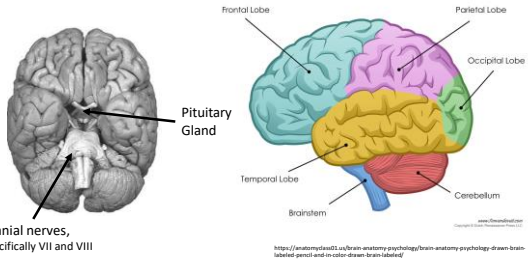
Location



Incidence

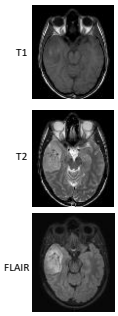


Brain tumor regions[1,3,51]



Diagnosis[1,3]

- MRI with IV contrast is the only diagnostic test required
- Can do CT for those who cannot perform MRI
- Biopsy or surgical resection to determine histological diagnosis
  - CNS lymphoma
  - Areas where resection is difficult are biopsied to assess for risk



Brain Tumors[1,3]

TYPE	SURVIVAL	TREATMENT
Metastatic - often from lung, melanoma, renal, breast	1-2 months if left untreated Studies show improvement of survival by 4-6 months following WBRT Up to 50% have new lesions within 6 months of initial treatment	WBRT most common but comes with significant cognitive side effects Other options include: stereotactic radiosurgery, surgical resection, systemic treatment
Meningiomas	Usually benign, rarely anaplastic	Usually surgically resectable, meds for seizures

Brain Tumors- Gliomas[1,3]

TYPE OF GLIOMA	SURVIVAL	TREATMENT
Glioblastoma (GBM) (Grade IV)	35% 1y, 4.7% 5y survival. 2y- 27% with TMZ vs 10% w/out Bevacizumab inc progression-free survival but not overall survival.	Surgical resection for relieving mass effect. Radiation therapy. TMZ. Implantable biodegradable polymers Bevacizumab - targeting angiogenesis
Anaplastic Astrocytoma (III)	Median survival 2-3y 60%, 5y 25.9%	Similar to glioblastoma: surgical resection, radiation therapy; TMZ often used
Low Grade Glioma (II-I)	II- 72% 1y, 47% 5y I- Best when completely resectable 91% 10y survival	Surgical resection; sometimes radiation therapy, especially if incomplete resection
Oligodendro-glioma	94% 1y; 79% 5y (if anaplastic type 81%/49%)	Surgical resection; Radiation therapy; Chemotherapy
Mixed glioma	88% 1y; 60% 5y survival	Surgical resection; sometimes chemotherapy (such as TMZ), or radiation

Brain tumors cont. [1,3]

TYPE	SURVIVAL	TREATMENT
Ependymoma	82% 5y survival May be benign or malignant 10-15% may spread within CNS	Surgical resection, sometimes radiation or chemotherapy
Pituitary	Usually benign, very rarely malignant	Surgical resection
Nerve sheath tumors	Usually benign, very rarely malignant	Monitoring vs surgical resection
Primary CNS lymphoma	48% 1y, 28% 5y survival	Better survival with chemotherapy, +/- radiation than resection
Leptomeningeal Disease	Median survival 10-12 wk	May include supportive care, intrathecal chemotherapy alone or +/- systemic chemotherapy or radiation

Primary CNS Lymphoma

- A rare non-Hodgkin lymphoma in which malignant cells form in the lymph tissues of the brain, leptomeninges, and/or spinal cord
- ~1,500 new cases of PCNSL are diagnosed in the United States each year[52]
  - 2% of all non-Hodgkin lymphomas
  - Higher incidence in immunocompromised patients
- Mean survival of 44 months after diagnosis when treated with chemotherapy +/- radiation[53,54]
- 5 year survival of 30% in immunocompetent patients
  - Prognosis depends significantly on age
- Symptoms depend on location of the tumor[53,54]
  - Frontal lobes and deep periventricular brain structures are most common

Primary CNS Lymphoma

- First line treatment is systemic chemotherapy with a high dose methotrexate regimen[55,56]
- WBRT is most often used for residual disease after chemotherapy[55,56]
  - Avoided as first line treatment if possible due to high incidence of severe treatment related delayed neurocognitive decline, particularly in those >60 y.o.
    - 25-35% at 5 years in patients treated with HD-MTX and WBRT[55]
- Autologous stem cell transplants are an emerging treatment option[57]
- Surgical resection not typically used for CNS lymphoma due to widespread and diffusely infiltrative tumor growth[55]

Leptomeningeal Disease

- Also called leptomeningeal metastases or leptomeningeal carcinomatosis
- A rare complication of advanced cancer in which the disease spreads to the membranes (meninges) surrounding the brain and spinal cord
- Associated with poor prognosis[58,59]
  - Untreated, median survival is 4-6 weeks
  - Treated, median survival is 2-3 months
- Tends to occur most commonly with cancers that spread to the CNS[60]
  - Breast (12-35% of cases), lung (10-26%), melanoma (2-25%) (MD Anderson)
  - Primary brain tumors can also infiltrate the meninges and cause LMD
- Specific clinical signs and symptoms vary depending upon the site(s) of LMD[58]
  - Typically multifocal, indicative of multilevel involvement
  - Most common: headache, lower extremity weakness, ataxia, altered mental status, diplopia, and facial weakness or numbness
  - Hydrocephalus can occur from obstruction of CSF

Leptomeningeal Disease[61,62]

- Treatment is palliative with goal of stabilizing the disease, preserving neurological performance, and improving quality of life
  - Goal for improvement in symptoms must be balanced with potential side effects of treatment
- Radiation appears to be most effective for symptom relief
  - Whole brain or more focal areas of brain/spine causing the most symptoms
  - Craniospinal radiation may be considered for patients with higher performance status but can be highly toxic
- Chemotherapy
  - Typically only offered to patients with high performance status
  - Intrathecal delivery is more common due to lower toxicity compared with systemic chemotherapy
- Corticosteroids for symptomatic relief
- VP shunting can be effective in palliating symptoms from hydrocephalus

Brain Metastases[63]

- Occur in 10-30% of adults with cancer
  - Lung: 16-20%; Melanoma: 7%; Renal Cell: 7-10%; Breast: 5%
- Clinical manifestations include:
  - Headache (40-50% of the time)
  - Focal neurologic dysfunction (20-40%)
  - Cognitive dysfunction (30-35%)
  - Seizures (10-20%)
- Contrast-enhanced MRI is the most reliable imaging for detecting brain metastases, however biopsy may also be required
  - Differential diagnosis includes but is not limited to: primary brain tumor, infectious process, demyelination, cerebral infarct, or paraneoplastic phenomena

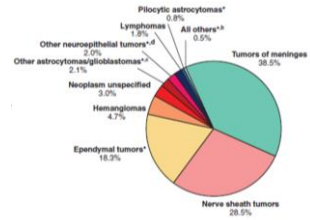
Brain Metastases

- Predictors of survival are performance status (often using KPS), age (<65yrs), number of metastases and extent of extracranial disease[64]
- If left untreated, median survival is 1-2 mo[64]
- Treatment Options[64, 65]
  - Systemic therapy
  - Radiation
  - Surgical Resection
  - Symptom Management
  - No Treatment: Systemic progression of disease with few treatment options and poor performance status
- Up to 50% of patients have new lesions within 6 months of initial treatment[64]

Brain Metastases[65]

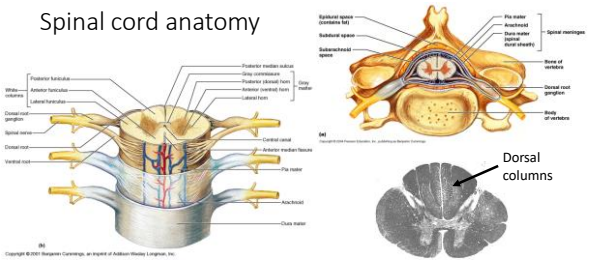
TREATMENT OPTION	INDICATION FOR TREATMENT
Systemic Therapy	Brain Metastasis (BM) found on screening for planned systemic treatment BM from highly chemotherapy-sensitive primary cancer
Whole Brain Radiation Therapy	Multiple BMs, especially for a primary tumor is radiotherapy sensitive Large BMs not amenable to SRS CNS and systemic progression of disease with poor performance status Salvage therapy for recurrent BM Postsurgical resection of a dominant BM with multiple remaining BMs
Stereotactic Radiosurgery	Oligometastases (OM) or multiple BMs when a primary tumor is radiotherapy resistant Postsurgical resection of a single BM Local relapse after surgical resection of a single BM Salvage therapy for recurrent OM after WBRT
Surgical Resection	Uncertain diagnosis of CNS lesion 1-2 BMs, especially when associated with extensive cerebral edema Dominant BM is in a critical region

Spinal Tumor locations[51]



Distribution of Spinal Cord, Spinal Meninges and Cauda Equina Tumors in Adults (+20).

Spinal cord anatomy



Diagnosis[2,3]

- Early detection and management of spinal cord compression is important to prevent permanent complications
  - X-ray – over 50% of the bone must be destroyed to be visible on plain films
  - CT shows bone and soft tissue changes
  - MRI best because shows bone/soft tissue, cord, and epidural space. Also shows multiple mets if present which impacts treatment

MRI imaging of spinal tumors[2]

Epidural tumor with SC compression

Intradural Extramedullary

Intradural Intramedullary

Spinal tumor table[2,3]

LOCATION	INCIDENCE	SURVIVAL	TREATMENT
Extradural (Epidural)	2-5% of pts develop ESCC (epidural spinal cord compression	More commonly malignant	corticosteroids alleviate pain and preserve neurologic function and continued through radiation Radiation is early treatment with spinal cord compression – up to 8-% demonstrate a response Surgery
Intradural Extramedullary	Mets in 3-8% of all pts	Most commonly benign	surgical intervention, radiation therapy, chemotherapy, and hormonal manipulation.
Intradural Intramedullary	4-5% of all primary CNS tumors	Mostly benign	surgical intervention, radiation therapy, chemotherapy, and hormonal manipulation.

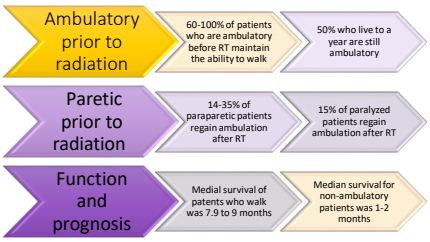
Spinal Mets – Medical Intervention[67]

- 12,700 patients with cancer in the US develop spinal cord compression per year
  - Breast, prostate, and lung cancer each account for 15% to 20% of cases
  - non-Hodgkin lymphoma, myeloma, and renal cell carcinoma each account for 5% to10% of cases
- Treatment:
  - Pain medications
  - Corticosteroids to decrease vasogenic edema
  - Radiation therapy – directed at painful vertebral mets or subclinical spinal cord compression
    - Used alone improved pain in 74-89% of pts and none developed spinal instability or neurological defects
    - Doses are designed to have less than 5% chance of inducing a radiation myelopathy (hemiparesis, spasticity, loss of pain and temp sensation)

Spinal Met Medical Intervention – Outcomes[67]

- Conservative Treatment
  - No significant change in pain (77.4% with mild to no pain)
  - 3.9% improvement of paralysis
  - Minimal change in Barthel Index; mean duration of effects were 49.7% of survival time
- Palliative Surgery
  - 93.6% with mild to no pain
  - 81.6% improvement of paralysis
  - 14.8 mean improvement in Barthel Index (significant); mean duration of effects were 53.7% of survival period
- Excisional Surgery
  - 96.3% with mild to no pain
  - 70% improvement of paralysis
  - Highest functioning on Barthel Index (86.4) but no significant change; mean duration of effects were 72.6% of survival time

"Will I walk again?" [67]



Spinal Mets - Functional Prognosis

- Functional Prognosis[67]
  - lung cancer mets are least likely to retain the ability to walk
  - no radiation protocol has been superior in maintaining/preserving ambulation
  - Surgery plus radiation maintained ambulation for a significantly longer period than patients who were randomized to radiation alone
  - Ambulation pre-radiation and time from development of motor deficits to radiation are the most important predictors of ambulation after treatment
- Functional Prognosis depends on the survival period irrespective of the treatment modality. So the functional outcome is determined by the survival period, not the type of intervention[68]

Neuroplasticity

2. Apply the principles of neuroplasticity to the rehabilitation of patients with neuro-oncologic diagnoses.

Neuroplasticity[69]

- Definition
  - Ability of neurons to change function, chemical profile or structure
  - Can be adaptive or maladaptive
- Adaptive functional changes allow:
  - Memorization of new fact or mastery of new skill
  - Adjustment to new environment
  - Recovery from injury

Neuroplasticity principles[69]

1. Use it or lose it
2. Use and Improve it
3. Specificity
4. Repetition Matters
5. Intensity Matters
6. Salience Matters
7. Time Matters
8. Age Matters
9. Transference
10. Interference

Factors that affect plasticity[69, 70]

- Experience (activity)
- Sleep
- Mood
- Hormones
- Cardio-respiratory function
- Nutrition
- Pharmaceuticals

Neg side effects of CA and CA tx[3]

- Experience (activity)
- Sleep
- Mood
- Hormone imbalance
- Cardio-respiratory function
- Nutrition
- Pharmaceuticals

Neuroplasticity and Intervention

- Planning treatment sessions
  - Prioritize treatment
    - Interventions that are task specific, intensive, repetitive and could create adaptations
  - Research based (with FITT guidelines)
    - Fqz, intensity, time, type
  - Measure progress and outcomes
  - Communication
    - Expectations
    - Might look worse than compensation pattern
    - Celebration of measurable results

Motor learning[70,71]

- Motor learning
  - Definition of motor learning: a set of processes associated with practice or experience, leading to relatively permanent changes in skilled behavior
- Declarative (Explicit) vs Procedural (Implicit) Learning
- Intrinsic vs Extrinsic Feedback
  - Knowledge of performance
  - Knowledge of results
- Practice conditions
  - Massed vs distributed
  - Constant vs variable
  - Blocked vs Random
  - Whole vs Part

Radiation's Impact on Plasticity[72]

- Radiation creates an environment hostile to plasticity
  - Damaged endothelial cells which create the blood brain barrier (BBB)
  - Allows increased proteins, cytokines, clotting factors, inflammatory cells and drugs across the BBB
  - Causes prolonged gliosis and glial scars, preventing axonal regeneration or remyelination
- After radiation see fewer neurons, a significant decrease in myelin, swelling of nerve fibers and increased thickening of the myelin sheaths indicative of dying axons

Neuro-Protective Benefits of Exercise[72]

- Exercise can improve:
  - white matter tracts
  - myelin
  - improve hippocampal density leading to improved cognition
  - Cortical gliogenesis
  - Increase growth hormone and reduce inflammation
  - Increase microglia (helps with cell proliferation)

Case Study Introduction - A

TREATMENT

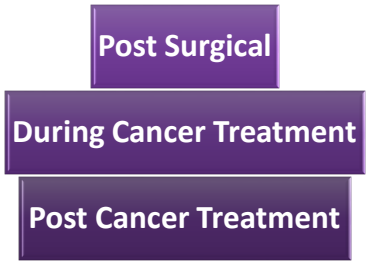
3. Prescribe a targeted exercise intervention for improving functional mobility in patients with neuro-oncologic diagnoses across the continuum of care.

4. Implement and modify physical therapy interventions based on the phase of a patient's medical course.

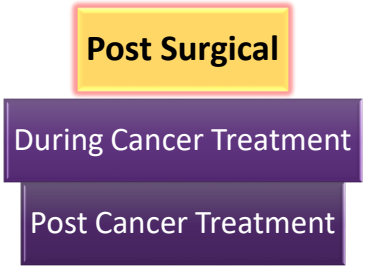
Case Study Introduction - B

"In the absence of any brain cancer specific data, health professionals should rely on the current guidelines for all cancer patients when providing exercise to this group."[73]

Phases of Cancer Treatment



Phases of Cancer Treatment



Acute SCI Exam

- Considerations:
  - Age
  - Prior cancer tx (primary spinal vs. Mets)
- Skin:
  - Older population
  - More fragile after chemotherapy or radiation
- BP:
  - Autonomic dysreflexia
  - TED hose, abdominal binders, ace wraps for BP support
- Strength:
  - To assess for change
  - Steroid myopathy
- Sensation:
  - For skin protection
  - Proprioception and light touch for balance
- Bowel and bladder
  - Neurogenic
  - Skin integrity
- Cardiovascular/Endurance
  - Deconditioning from prior cancer interventions
- Stability of the spine
  - TLSO, C-collar
- Special considerations with cancer related SCI
  - Prognosis related to ethics of equipment and progression of mobility concerns
- Fracture risk
  - Mets, multiple myeloma

Brain/Neuro Exam

- Considerations
  - Age
  - Prior cancer treatments (primary brain tumor vs. Mets)
- Tumor location
  - Neighboring structures
  - Neuroanatomy
- Vision/Neglect
  - Awareness of surroundings
- Strength
  - To assess for change
  - Steroid myopathy
- Sensation:
  - For skin protection
  - Proprioception and light touch for balance
- Cranial Nerves
  - Especially in brainstem
  - Nerve sheath tumors
- Coordination
  - Cerebellar involvement
  - Due to weakness
- Cognition
  - MOCA
  - STM/orientation
  - pathfinding
- Cardiovascular/Endurance
  - Deconditioning from prior cancer interventions

When to Advocate for SLP Consult

- Impairments in cognition
  - Short or long term memory
  - Attention (distractibility, poor topic maintenance)
  - Problem solving (following instructions, impulsive behaviors)
  - Organization (sequencing)
- Impairments in speech
  - Unintelligible or patient is frustrated by the way their speech has changed
- Impairments in language
  - Comprehension, verbal expression, social communication, reading or writing

PT Goals of Care

- Rehab goals post-surgery and pre-adjuvant therapy[74]
  - Early mobilization helps prevent complications of immobility
    - VTE, skin breakdown, contracture development, constipation, orthostasis, pneumonia
  - Self-care activities should be encouraged in stable brain tumor patients
    - Early participation in self-care increases strength, endurance, awareness, communication, problem solving, and social activity

Distress in Early Diagnosis and Treatment[75]

- Patients with brain tumors report a greater number of problems than patients with other cancers
  - Major problems include mobility and neuropsychological functioning
- Karnofsky score is significantly, negatively correlated with the number of practical problems
- Awareness of the diagnosis/prognosis did not impact distress scores

Fatigue After Surgery

- Fatigue is very common in post-surgical patients with primary brain tumor even before starting chemotherapy and radiation
  - 48% of patients with glioblastoma[76]
- Postoperative fatigue is at its peak during the first month after surgery but can persist even one year after surgery for general oncology populations[77]
  - Etiology of postoperative fatigue is unclear, but similar contributors to CRF are suspected

Outcomes After Inpatient Rehabilitation

Brain tumor compared to CVA[78,79]

- Location matched
- No significant difference in level of function at admission or discharge
  - Both groups made similar, significant gains
  - No difference in length of stay on inpatient rehabilitation unit

Outcomes After Inpatient Rehabilitation

- Brain tumor vs. TBI[80]
- Patients with TBI had lower functional level prior to inpatient rehab compared to postoperative patients with high grade gliomas
  - No significant difference between TBI and brain tumor patients at discharge, therefore TBI pts had greater rate of change in functional gains during inpatient rehab
  - Length of stay was significantly longer for TBI pts (median of 6 days for patients with brain tumor, 20.5 days for TBI).
  - No significant difference in functional outcome or LOS based on brain lesion side

Spine (SCI to tumor research) [81,82]

- Patients with spinal cord compression who receive rehabilitation have increased satisfaction with life, less depression, and persistent decreases in pain
- Average length of inpatient rehabilitation was 27 days
- 84% of patients were discharged to home
- Mobility, ambulation, self-care, and transfer abilities persisted for at least 3 months following discharge

Post Surgical Interventions[78,79,83]

- Interventions provided to those admitted to inpatient rehabilitation (IPR)
  - At least 5 days per week, 1-1.5 hours per day
- Each of the research studies tailored the interventions to the needs of the patient and their impairments.
- Without specific evidenced based interventions for cancer populations, defer to the neuroplasticity research for neurologic populations

Neuro research

High Intensity gait training, CVA[84,85]

- F: 5 days/week, 1 hour session
- I 70-80% HR reserve/RPE 15-17
- T: 10 mins of speed dependent training, skill dependent treadmill training, overground training, stair training at highest speed tolerated within HR parameters
- T: 1-6 months post CVA

- Improved gait speed and 6MWT and gait kinematics

High Intensity Interval Training (HIIT) [86]

- Performed across the continuum of care
  - F: 30-60sec intervals, 16-60 minutes total (including rest), 2-3 times per week
  - I: 60-85% range, progressed every 1-2 weeks
  - T: varied strength and aerobic exercises
  - T: 4-20 weeks – most had a 4 week introduction period
- Improved aerobic capacity, decreased body mass, body fat, hip and waist circumference, improved strength in several studies
- Time efficient dose of exercise
- Highly compliant – 89% average across studies

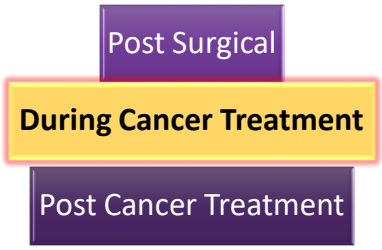
Post Surgical Take Home Messages

- Perform a thorough assessment
- Consider the patient's upcoming cancer therapy
- Brain tumor patients have similar outcomes to patients with acquired brain injury
- Should be provided with a tailored physical therapy program
- "In the absence of any brain cancer specific data...rely on the current guidelines for all cancer patients when providing exercise to this group." Cormie et al.

Pre-Cancer Treatment Case Study - A

Pre-Cancer Treatment Case Study - B

Phases of Cancer Treatment



Functional Capacity During Treatment

- Jones et al. propose more clinical measures that are more specific to the challenges to patients undergoing adjuvant therapy with high grade gliomas[87]
  - Impacted by radiation, chemotherapy, chronic steroid use
- Assessed:
  - Muscle cross sectional area
  - VO2max, HRmax
  - QoL and fatigue
  - Body composition
- Each functional performance measure declined over the 24 weeks after surgical resection
- Exercise initially increased during first 6 weeks, then declined at 24 weeks

Exercise Feasibility with Brain Tumor[88]

- Patients with high grade gliomas undergoing adjuvant therapy
- HEP including:
  - F: daily
  - I: low: red theraband, walking without exertion
  - T: 3 strengthening exercises, 1 balance exercise, walking
  - T: 28 days started first week of radiation
- High compliance
- No adverse events

Exercise and Fatigue[89]

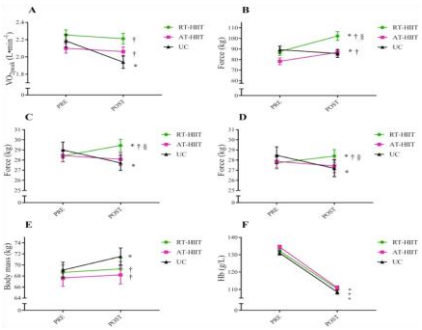
- Patients with variety of cancers, including brain tumors, undergoing adjuvant therapy
  - F: 6days/week: 4 days of low intensity exercise , 3 days of high intensity exercise
  - I:
    - High intensity: 45 mins resistance training 70-100% 1RM and 15 mins of cardiovascular exercise at 85-95% HR max on a stationary bike
    - Low Intensity: Relaxation 30mins 4 times per week : relaxation, massage, body awareness training
  - T: resistance training, stationary bike
  - T: throughout adjuvant therapy
- Significant decline in fatigue
- Patient with a brain tumor had a seizure – recommend against high intensity exercise

Exercise and Fatigue[90]

- Patients with breast cancer
- Started during the first week of radiation
- Supervised more effective than unsupervised exercise
  - F: aerobic 3 days/week, Strengthening 2 days/week
  - I: 50-75% Hrmax, 60-80% 1RM
  - T: aerobic, strengthening
  - T: 20-60mins, 8-12 repetitions
- Significant reduction in fatigue with comprehensive program
- Slight improvement, but not significant, change in fatigue with low intensity exercise

HIIT During Chemotherapy[91]

- Breast cancer patients, during chemotherapy
  - F: 2 sessions/week, 16 weeks
  - I: strengthening 80%/RPE 13-15 Borg Scale
  - T: 8-12 reps/20 minutes continuous
  - T: strengthening/aerobic
- Weak inverse relationship between fatigue and improved strength
- Improved strength, VO2max, more stable BMI, similar declines in blood values



Chemotherapy Induced Cardiomyopathy: Clinical Implications

- Aerobic exercise has had beneficial effects on chemotherapy induced cardiotoxicity in animal models[92, 93]
- Exercise guidelines for patients with cardiomyopathy and heart failure in the general population are recommended[94-96]
- Warm-up and cool-down
  - Monitor vitals before, during, and after to evaluate exercise tolerance
  - Start with shorter sessions and increase gradually
  - Pacing and use of RPE is very important

Chemotherapy Induced Cardiomyopathy: Clinical Implications[97,98]

ACSM recommendations for patients with heart failure:

F: 3-4 days/wk, increasing to 5 days/wk

I: Low to moderate initially, modified RPE $\leq$4/10

T: Start with 10-15 minute sessions and increase gradually. Goal of eventually accumulating 30-60 minutes per day

T: Start with low impact activities (e.g. brisk walking, cycling). Add high repetition, low intensity circuit resistance training 2-3 days/wk

Exercise and Spinal Mets[81,82]

- Performed in patients with thoracic and lumbar mets
- **Exercise Group**: Supervised
  - F: exercise 5x/wk for 2 weeks, ~30min/session then cont HEP 3x/wk for 12 weeks,
  - I: isometrics with emphasis on neutral spine
  - T: 5 week supervised/12 weeks HEP
  - T: quadruped shoulder flexion 2x10 B, bridges 2x10, hooklying B leg lifts 2x4-8.
- **Control group**: Respiration exercises for ~15 min and "hot roll" treatments 5x/wk for 2 weeks
- Significantly impacted:
  - Fatigue
  - Psychological distress
  - Psychosocial aspects of QOL
- Not significantly different in survival time.
- No adverse events or pathological fractures

Exercise Preferences and Motivation[99]

- Patients with brain mets have limited interest in participating in physical activity
- Do believe that exercise is beneficial
- Preferences:
  - Exercising with friends or family
  - Exercising at home
  - Exercise in the morning
  - 20-30 minutes
  - Most interested in walking

Physical Therapy Plan of Care

- Conflicting data on whether radiation concurrent with the rehabilitation stay is associated with better or worse outcomes.
- Goals of care:
  - Prevent secondary complications
  - Reduce neurologic impairments
  - Teach compensatory techniques as needed
  - If severe cognitive impairment, affecting learning, or poor prognosis the focus is on family training

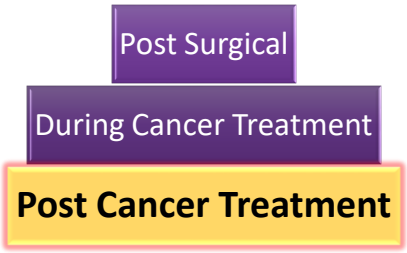
During Cancer Treatment: Take Home Messages

- Will see decreases in strength, aerobic capacity, increased fatigue during this phase of medical treatment
- Consider HIIT to improve strength and aerobic capacity
- Patients may need more motivation to participate in exercise during this phase of medical treatment
- Exercise can improve fatigue
- It can be safe to perform isometrics and core exercise with pts with stable spinal mets

During Cancer Treatment Case Study - A

During Cancer Treatment Case Study - B

Phases of Cancer Treatment



Neuroplasticity, Cognition, and Exercise

- Performed in rats, 3-4 weeks after chemotherapy[101]
  - F: 6-7 days per week , 30 mins
  - I: low intensity – simulates human exercise, TM with 5 min warm up at 0* incline, 3m/min, exercise at 10m/min, 5 min cool down
  - T: treadmill exercise
  - T: starting 3-4 233ks after chemotherapy, for 4 weeks
- Cognitive decline in working memory and spatial awareness in all subjects with chemotherapy[101]
- With exercise see an increased capacity for short term memory, faster rate of improvement in spatial learning[101]
- Exercise improves hippocampal and cognitive function, as well as neuroplasticity[100,101]

Cognitive effects of exercise

Yoga can improve self-reported memory deficits, QoL and reduce fatigue in pts with breast cancer[102]

- F: 2x/week for 4 weeks
- I: low intensity/restorative yoga
- T: YOCAS consists of gentle Hatha yoga, meditation, breathing exercises and restorative yoga postures.
- T: 2-24 months post adjuvant therapy

- Self-reports indicate physical activity is correlated with an improvement in cognitive function and a reduction in distress and fatigue[105]

Outpatient PT and CA[103,104]

- Limited research on outpatient PT and pts with cancer
  - 2 articles on outpatient multidisciplinary rehab (MDR)
    - Interdisciplinary outpatient rehabilitation services showed overall stable HRQOL, pain, and depression at the conclusion of rehabilitation and 3 mos later [103]
    - Some evidence to support MDR for improved 'activity' in BT survivors in the shorter-term[104]
    - More research in the effectiveness of 'specific' rehabilitation interventions and participation domains is needed.
    - Issues with feasibility
      - 2-3x/wk for 8wks, 2hrs/day (PT, OT, Pscyh and social group)
      - 2-5x/wk for 6mo, 4-8hrs/day (PT, OT, Speech) various "tracks"

Post Adjuvant Therapy: Take Home Messages

- Delayed effects of cancer treatment can develop months to years after treatment is completed
  - Radiation myelopathy
  - CIPN
  - Cardiomyopathy
  - Fatigue
  - Cognitive changes
- Minimal amounts of aerobic exercise can have a positive impact on cognitive function, QoL, and fatigue
- Feasibility of multidisciplinary outpatient treatment

Post Cancer Treatment Case Study - A

Post Cancer Treatment Case Study - B

Differences in Patients with Neurological vs Cancer Diagnoses

- Differences between CVA and BT chronically
- Fluctuation between repeated medical interventions
- More likely to be readmitted to acute care/go home with hospice
- Rapid changes to medical and functional status

Clinical pearls/considerations

In absence of research follow CVA/BI or SCI research intervention recommendations

Consider cancer related fatigue

Neuroplasticity is affected by chemo and tumors – try to maximize with exercise and training

High intensity rehab can be good for cancer patients

Metastatic cancer has poor prognosis, consider GOC

References

1. Vargo MM. Brain tumors and metastases. Phys Med Rehabil Clin N Am. 2017; 28: 115–141. http://dx.doi.org/10.1016/j.pmr.2016.08.005
2. Ruppert LM. Malignant spinal cord compression. Phys Med Rehabil Clin N Am. 2017; 28: 101–114. http://dx.doi.org/10.1016/j.pmr.2016.08.007
3. Stubblefield MD, O'Dell MW. Cancer Rehabilitation: Principles and Practice. New York, NY: Demos Medical Publishing: 2009.
4. Itano JK. Core Curriculum for Oncology Nursing. 5th edition. St Louis, MO: Elsevier: 2016.
5. Becht LD, van den Bent M, Shih HA. Management of low-grade gliomas in adults. In: Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed November 18, 2018.
6. Batchelor T. Initial postoperative therapy for glioblastoma and anaplastic astrocytoma. In: Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed November 18, 2018.
7. Steingart RM, Yadav N, Manrique C, Carver JR, Liu J. Cancer survivorship: cardiotoxic therapy in the adult cancer patient; cardiac outcomes with recommendations for patient management. *Semin Oncol*. 2013;40(6):690-708.
8. Curigliano G, Cardinale D, Dent S, et al. Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. *CA Cancer J Clin*. 2016;66(4):309-325.
9. Aronzi A, Nelles TG, Tripathy D, Scherrer-Crosbie M. Clinical manifestations, monitoring, and diagnosis of anthracycline-induced cardiotoxicity. In: Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed November 16, 2018.
10. Nelan TG, Aznaci A, Tripathy D, Scherrer-Crosbie M. Prevention and management of anthracycline cardiotoxicity. In: Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed November 16, 2018.
11. Lien CY, Jensen BT, Hydock DS, Hayward R. Short-term exercise training attenuates acute doxorubicin cardiotoxicity. *J Physiol Biochem*. 2015;71(4):669-678.
12. Jensen BT, Lien CY, Hydock DS, Schneider CM, Hayward R. Exercise mitigates cardiac doxorubicin accumulation and preserves function in the rat. *J Cardiovasc Pharmacol*. 2013;62(3):263-269.
13. Feldman D, Vander Els N. Bleomycin-induced lung injury. In: Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed November 30, 2018.
14. Balk RA. Methotrexate-induced lung injury. In: Post T, ed. *UpToDate*. Waltham, Mass.: *UpToDate*; 2018. www.uptodate.com. Accessed November 30, 2018.
15. LaCasce AS. Therapeutic use and toxicity of high-dose methotrexate. In: Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed November 30, 2018.

References

16. Lee EQ. Overview of neurologic complications of platinum-based chemotherapy. In: Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed December 2, 2018.
17. Langer T, am Zehnhoff-Dinnesen A, Radtke S, Meitert J, Zolk O. Understanding platinum-induced ototoxicity. *Trends Pharmacol Sci*. 2013;34(8):458-469.
18. Starobova H, Vetter I. Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. *Front Mol Neurosci*. 2017;10:174-189.
19. Hou S, Huh B, Kim HK, Kim KH, Abdi S. Treatment of Chemotherapy-Induced Peripheral Neuropathy: Systematic Review and Recommendations. *Pain Physician*. 2018;21(6):571-592.
20. Loprinzi CL. Prevention and treatment of chemotherapy-induced peripheral neuropathy. In: Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed December 2, 2018.
21. Merchan JR, Jhaveri KD. Chemotherapy nephrotoxicity and dose modification in patients with renal insufficiency: Conventional cytotoxic agents. In: Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed November 29, 2018.
22. Simo M, Rifa-Ros X, Rodriguez-Fornells A, Bruna J. Chemobrain: a systematic review of structural and functional neuroimaging studies. *Neurosci Biobehav Rev*. 2013;37(8):1311-1321.
23. Vitali M, Ripamonti C, Rollo F et al. Cognitive impairment and chemotherapy: a brief overview. *Crit Rev Oncol Hematol*. 2017;118:7-14.
24. Li M, Caeyenberghs K. Longitudinal assessment of chemotherapy-induces changes in brain and cognitive functioning: a systematic review. *Neurosci Biobehav Rev*. 2018;92:304-317.
25. Hodgson K, Hutchinson A, Wilson C, Nettlebeck T. A meta-analysis of the effects of chemotherapy on cognition in patients with cancer. *Cancer Treat Rev*. 2013;39(3):297-304.
26. Vargo M. Brain tumor rehabilitation. *Am J Phys Med Rehabil*. 2011;90(5 Suppl 1):S50-62.
27. Correa D, DeAngelis L, Shi W et al. Cognitive functions in survivors of primary central nervous system lymphoma. *Neurology*. 2004;62(4):548-55.
28. Escalante CP. Cancer-related fatigue: Prevalence, screening and clinical assessment. In: Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed October 15, 2018.
29. Ashar A, Fu JB, Bailey C, Hughes JK. Fatigue among patients with brain tumors. *CNS Oncol*. 2016;5(2):91-100.
30. Kim BR, Chun MH, Han EY, Kim DK. Fatigue assessment and rehabilitation outcomes in patients with brain tumors. *Support Care Cancer*. 2012; 20(4):805-812.

References

31. Valko PO, Siddique A, Linsenmeier C, Zaugg K, Held U, Hofer S. Prevalence and predictors of fatigue in glioblastoma: a prospective study. *Neuro Oncol*. 2015;17(2):274-281.
32. Van Waart H, Stuiver MM, van Harten WH, et al. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: Results of the PACES randomized clinical trial. *J Clin Oncol*. 2015;33(17):1918-1927.
33. Dennett AM, Peiris CL, Shields N, Prendergast LA, Taylor NE. Moderate-intensity exercise reduces fatigue and improves mobility in cancer survivors: a systematic review and meta-regression. *J Physiother*. 2016;62(2):68-82.
34. Hojan K, Kwiatkowska-Borowczyk E, Leporowska E, et al. Physical exercise for functional capacity, blood immune function, fatigue, and quality of life in high-risk prostate cancer patients during radiotherapy: a prospective, randomized clinical study. *Eur J Phys Rehabil Med*. 2016;52(4):489-501.
35. Kummer F, Catuogno S, Perneus JM, Bloch W, Baumann FT. Relationship between cancer-related fatigue and physical activity in inpatient cancer rehabilitation. *Anticancer Res*. 2013;33(6):3415-3422.
36. Nakano J, Hashizume K, Fukushima T. Effects of aerobic and resistance exercises on physical symptoms in cancer patients: A meta-analysis. Integr Cancer Ther. 2018;17(4):1048-1058.
37. Hilfiker R, Meichtry A, Eicher M, et al. Exercise and other non-pharmaceutical interventions for cancer-related fatigue in patients during or after cancer treatment: a systematic review incorporating an indirect-comparisons meta-analysis. *Br J Sports Med*. 2018;52(10):651-658.
38. Tian L, Lu HJ, Lin L, Hu Y. Effects of aerobic exercise on cancer-related fatigue: a meta-analysis of randomized controlled trials. *Support Care Cancer*. 2016;24(2):969-983.
39. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev*. 2012;(11):CD006145. doi: 10.1002/14651858.CD006145.pub3.
40. Kessels E, Husson O, van der Feltz-Cornelis CM. The effect of exercise on cancer-related fatigue in cancer survivors: a systematic review and meta-analysis. *Neuropsychiatr Dis Treat*. 2018;14:479-494.
41. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev*. 2012;(8): CD008465. doi: 10.1002/14651858.CD008465.pub2.
42. Jarden M, Baandrup-Gadsbøll MT, Hovgaard DJ, Boesen E, Adamsen L. A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance, and quality of life in adult patients undergoing allogeneic SCT. *Bone Marrow Transplant*. 2009;43(9):725-737.
43. Oechsle K, Aslan Z, Suesse Y, Jensen W, Bokemeyer C, de Wit M. Multimodal exercise training during myeloablative chemotherapy: a prospective randomized pilot trial. *Support Care Cancer*. 2014;22(1):63-69.
44. Dittus KL, Gramling RE, Ades PA. Exercise interventions for individuals with advanced cancer: A systematic review. *Prev Med*. 2017;104:124-132.
45. Heywood R, McCarthy AL, Skinner TL. Efficacy of exercise interventions in patients with advanced cancer: A systematic review. *Arch Phys Med Rehabil*. 2018;99(12):2595-2620.

References

46. Mijwel S, Backman M, Bolam KA, et al. Highly favorable physiological responses to concurrent resistance and high-intensity resistance and high-intensity interval training during chemotherapy: the OptiTrain breast cancer trial. *Breast Cancer Res Treat.* 2018;169(1):93-103.
47. Kampshoff CS, Chinapaw MJ, Brug J, et al. Randomized controlled trial of the effects of high intensity and low-to-moderate intensity exercise on physical fitness and fatigue in cancer survivors: results of the Resistance and Endurance Exercise After ChemoTherapy (REACT) study. *BMC Med.* 2015;13:275-288.
48. Adams SC, DeLorme DS, Davenport MH, Fairey AS, North S, Courneya KS. Effects of high-intensity interval training on fatigue and quality of life in testicular cancer survivors. *Br J Cancer.* 2018;118(10):1313-1321.
49. Andersen C, Ibarth M, Ejlertsen B, et al. The effects of a six-week supervised multimodal exercise intervention during chemotherapy on cancer-related fatigue. *Eur J Oncol Nurs.* 2013;17(2):331-339.
50. De Backer IC, Vreugdenhil G, Nijziel MR, Kester AD, van Breda E, Schep G. Long-term follow-up after cancer rehabilitation using high-intensity resistance training: persistent improvement of physical performance and quality of life. *Br J Cancer.* 2008;99(1):30-36.
51. Ostrom QT, Gittleman H, Truitt G, et al. CBTRUS statistical report: primary brain and other centeral nervous system tumors diagnosed in the US in 2011-2015. Neuro Onc. 2018; 20(54):1-86. doi:10.1093/neuonc/noy131
52. National Cancer Institute. Cancer Stat Facts: Non-Hodgkin Lymphoma. https://seer.cancer.gov/statfacts/html/nhl.html. Accessed November 13, 2018.
53. Batchelor T, Loeffler JS. Clinical presentation, pathologic features, and diagnosis of primary central nervous system lymphoma. In: Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed November 2, 2018.
54. Kerbauy MN, Moraes FY, Lok BH. Challenges and opportunities in primary CNS lymphoma: A systematic review. *Radiother Oncol.* 2017;122(3):352-361.
55. Grommes C, DeAngelis LM. Primary CNS lymphoma. *J Clin Oncol.* 2017;35(21):2410-2418.
56. Batchelor T. Treatment and prognosis of primary central nervous system lymphoma. In: Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed November 2, 2018.
57. Ferreri AJ, Illerhaus G. The role of autologous stem cell transplantation in primary central nervous system lymphoma. *Blood.* 2016;127(13):1642-1649.
58. Demopoulos A. Clinical features and diagnosis of leptomeningeal metastases from solid tumors. In:Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed November 2, 2018.
59. Stubblefield MD, O'Dell MW. Cancer Rehabilitation: Principles and Practice. New York, NY: Demos Medical Publishing; 2009.
60. MD Anderson Center. New hope for leptomeningeal disease care. https://www.mdanderson.org/publications/cancerwise/2017/04/new-hope-for-leptomeningeal-disease-care.html. Accessed December 1, 2018.

References

61. Leal T, Chang JE, Mehta M, Robins HI. Leptomeningeal metastasis: challenges in diagnosis and treatment. *Curr Cancer Ther Rev.* 2011;7(4):319-327.
62. Demopoulos A, Brown P. Treatment of leptomeningeal metastases (carcinomatous meningitis). In: Post T, ed. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed November 2, 2018.
63. Loeffler J. Epidemiology, clinical manifestations, and diagnosis of brain metastases. In: UpToDate, Wen P, Eichler A, (Ed), UpToDate Waltham, MA. (Accessed on November 30, 2018.)
64. Loeffler J. Overview of the treatment of brain metastases. In: UpToDate, Wen P, Eichler A, (Ed), UpToDate Waltham, MA. (Accessed on November 30, 2018.)
65. Lin X, DeAngelis L. Treatment of brain metastases. *J Clin Oncol. 2015; 33(20):3475-3483.*
66. Cole A, Scherwath A, Ernst G, et al. Self-reported cognitive outcomes in patients with brain metastases before and after radiation therapy. *Int J Radiat Oncol Biol Phys.* 2013;87(4):705-12.
67. Abrahm JL, Banffy MB, Harris MB. Spinal Cord Compression in Patients with Advanced Metastatic Cancer: All I Care About Is Walking and Living My Life. 2008; 299(8): 937-946
68. Tokuhashi Y, Ajiro Y, Umezawa N. Outcome of treatment for spinal metastases using scoring system for preoperative evaluation of prognosis. *Spine.* 2009;34(1):69-73.
69. Klein JA and Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech Lang Hear Res.* 2008;51(1):225-39. doi: 10.1044/1092-4388(2008/018).
70. Shumway-Cook A, Woollacott MH. Motor Learning and Recovery of Function. In: Motor Control: Translating Research into Practice. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2017: 21-43.
71. Schmidt RA and Wrisberg CA. Motor Learning and Performance: a situation-based learning approach. 4th ed. Champaign: Human Kinetics; 2008.
72. Rodgers S, Trevino M, Zawaski J, et al. Neurogenesis, exercise, and cognitive late effects of pediatric radiotherapy. *Neurol Plast.* 2013; 2013: 698528. doi: 10.1155/2013/698528.
73. Cormie P, Nowak A, Chambers S, et al. The potential role of exercise in neuro-oncology. Front Oncol. 2015;5:85. doi: 10.3389/fonc.2015.00085.
74. Kushner D, Amidei C. Rehabilitation of motor dysfunction in primary brain tumor patients. Neuroonccol Pract. 2015;2(4):185-91.
75. Goebel S, Stark A, Kaup L, et al. Distress in patients with newly diagnosed brain tumours. Psychooncology. 2011;20(6):623-30.

References

76. Valko P, Siddique A, Linzenmeier C, et al. Prevalence and predictors of fatigue in glioblastoma: a prospective study. Neuo Oncol. 2015;17(2):274-81.
77. Rubin G, Cleare A, Hotopf M. Psychological factors in postoperative fatigue. Psychosom Med. 2004;66(6):959-64.
78. Geler-Kulcu D, Gulsen G, Bayulkabra E, et al. Functional recovery of patients with brain tumor and acute stroke after rehabilitation: a comparative study. J Clin Neurosci. 2009;16(1):74-8.
79. Bartolo M, Zucchella C, Pace A, et al. Early rehabilitation after surgery improves functional outcome in inpatients with brain tumours. J Neurooncol. 2012;107(3):537-44.
80. Biligin S, Kose N, Karakaya J, et al. Traumatic brain injury shows better functional recovery than brain tumor: a rehabilitative perspective. Eur J Phys Rehabil Med. 2014;50(1):17-23.
81. Ref H, Akbar M, Keller M, et al. Quality of life and fatigue in patients with spinal bone metastases under combined treatment with resistance training and radiation therapy- a randomized pilot trial. Radiat Oncol. 2014;9:151.
82. Ref H, Jensen A, Bruckner T, et al. Isometric muscle training of the spine musculature in patients with spinal bony metastases under radiation therapy. BMC Cancer. 2011;11:482. doi: 10.1186/1471-2407-11-482.
83. Fu JB, Parsons HA, Shin KY, et al. Comparison of functional outcomes in low- and high-grade astrocytoma rehabilitation inpatients. Am J Phys Med Rehabil. 2010;89(3):205-12.
84. Holleran et al. Feasibility and potential efficacy of high intensity stepping training in variable contexts in subacute and chronic stroke. Neurorehabil Neural Repair. 2014; 28(7): 643-651.
85. Hornby et al. Variable Intensive Early Walking Poststroke (VIEWS): A Randomized Controlled Trial Neurorehabil Neural repair. 2016; 30(5): 440-450.
86. Toohey K, Pumpa K, McKune A, et al. High-intensity exercise interventions in cancer survivors: a systematic review exploring the impact of health outcomes. J Cancer Res Clin Oncol. 2012;144(1):1-12.
87. Jones et al. Changes in functional performance measures in adults undergoing chemoradiation for primary malignant glioma: a feasibility study.
88. Baime J, Omer Z, Varlotto J, Yunus S. Compliance and safety of a novel home exercise program for patients with high-grade brain tumors, a prospective observational study. Support Care Cancer 2015;7:25;2809-2814 Oncologist;15(6):638-647
89. Adamsen L, Quist M, Andersen C, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomized controlled trial. BMJ.
90. Lipsett et al. The impact of exercise during adjuvant radiotherapy for breast cancer on fatigue and quality of life: a systematic review and meta-analysis.Breat. 2017;32:144-155

References

91. Mijwel et al. Highly favorable physiological responses to concurrent resistance and high-intensity interval training during chemotherapy: the OptiTrain breast cancer trial. Breast Cancer Res Treat. 2018;169(1):93-103
92. Lien CY, Jensen BT, Hydock DS, Hayward R. Short-term exercise training attenuates acute doxorubicin cardiotoxicity. J Physiol Biochem. 2015;71(4):669-678.
93. Nair N, Gongora E. Heart failure in chemotherapy-related cardiomyopathy: Can exercise make a difference? BBA Clin. 2016;6:69-75.
94. Chen JJ, Wu PT, Middlekauff HR, Nguyen KL. Aerobic exercise in anthracycline-induced cardiotoxicity: a systematic review of current evidence and future directions. Am J Physiol Heart Circ Physiol. 2017;312(2):213-222.
95. Sturgeon KM, Ky B, Liboroki JR, Schmitz KH. The effects of exercise on cardiovascular outcomes before, during, and after treatment for breast cancer. Breast Cancer Res Treat. 2014;143(2):219-226.
96. Steingart RM, Yadav N, Manrique C, Carver JR, Liu J. Cancer survivorship: cardiotoxic therapy in the adult cancer patient; cardiac outcomes with recommendations for patient management. Semin Oncol. 2013;40(6)690-708.
97. Pescatello, L, Arena, R, Riebe, D, & Thompson, P (2013). ACSM's Guidelines for Exercise Testing and Prescription (9th ed., pp. 166-177). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013.
98. Exercise is Medicine. Exercising with Heart Failure. http://www.exerciseismedicine.org/assets/page_documents/EIM%20Re%20series_Exercising%20with%20Heart%20Failure.pdf. Accessed December 12, 2018.
99. Lowe et al. physical activity interests and preferences of cancer patients with brain metastases: a cross-sectional survey. BMC Pallat Care.2016;15:7
100. Ji JE, JS Li, Sun RS, et al. Forced Running Exercise Attenuates Hippocampal Neurogenesis Impairment and the neurocognitive deficits induced by whole brain irradiation via the BDNF-Mediated Pathway. Biochem Biophys Res Commun. 2014;443(2):646-51.
101. Park HS, Kim CJ, Kwak HB, et al. Physical exercise prevents cognitive impairment by enhancing hippocampal neuroplasticity and mitochondrial function in doxorubicin-induced chemobrain. Neuropharmacology. 2018; 133:451-61.
102. Janelsins MC, Peppone LJ, Heckler CE, et al. YOCAS yoga reduces self-reported memory difficulty in cancer survivors in a nationwide randomized control trial: investigating relationships between memory and sleep. Integ Cancer Ther. 2016;15(2):263-71.
103. Khan F, Amatya B, Drummond K, et al. Effectiveness of integrated multidisciplinary rehabilitation in primary brain cancer survivors in an Australian community cohort: a controlled clinical trial. J Rehabil Med 2014; 46: 754-760
104. McCarty S, Eickmeyer SM, Kocherginsky M et al. Health-Related Quality of Life and Cancer-Related Symptoms During Interdisciplinary Outpatient Rehabilitation for Malignant Brain Tumor. Am J Phys Med & Rehab 2017; 96(12): 852-60.
105. Phillips SM, Lloyd GR, Awick EA, McAuley E. Relationship between self-reported and objectively measures physical activity and subjective memory impairment in breast cancer survivors: Role of self-efficacy, fatigue, and distress. Psychooncology. 2017;26(9):1390-1399.